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DRUG EFFECTS UPON COGNITIVE PERFORMANCE UNDER STRESS

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AUGUST 1966

DIVISION OF PSYCHOBIOLOGY

INSTITUTE FOR RESEARCH

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DIVISION OF PSYCHOBIOLOGY
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Drug Effects Upon Cognitive Performance Under Stress

Paul M. Hurst and Marianna F. Weidner

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Summary

Three experiments were conducted to investigate possible drug enhancement of cognitive performance in non-fatigued humans. Manipulated variables included incentive, placebo effect, task difficulty level, and task input pacing, while experimental designs provided either between-subject or within-subject comparisons in a factorial or a Latin square design. Drugs examined for effectiveness were *d*-amphetamine, secobarbital, methylphenidate, chlordiazepoxide, *d*-amphetamine plus secobarbital, and *d*-amphetamine plus chlordiazepoxide.

The study was guided by the viewpoint that *drug enhancement of cognitive performance is achieved through mitigation of disturbing influences, rather than through direct facilitation of cognitive processes*. Two mitigating components were postulated: an anti-stress factor and an anti-boredom factor.

Cognitive abilities subjected to examination were highly paced short-term memory and simple arithmetic skill. Changes in mood state, judgment of performance and perception of time passage completed the behavioral characteristics assessed.

D-amphetamine groups were characterized by consistently improved performance over placebo and/or no drug groups in both cognitive tasks. In two of the three experiments significant increases were obtained. Also, in the third experiment, a 15 mg. dose, employed in addition to

the previous 10 mg. dose, resulted in even greater performance enhancement. *D*-amphetamine combination groups (either with secobarbital or chlordiazepoxide) demonstrated performance better than *d*-amphetamine or no drug groups, but not significantly so. Scores for the methylphenidate group did not differ from those for the no drug group, while chlordiazepoxide group scores were lower (non-significant). The secobarbital group's performance was significantly impaired.

Among the major drug effects upon experimental mood factors were increases in vigor, elation and boldness and a decrease in fatigue by *d*-amphetamine: increases in fatigue and elation by secobarbital; and increases in sadness and sociability by the *d*-amphetamine-chlordiazepoxide combination.

Neither time estimation nor judgment of performance was significantly affected by the drugs in this study.

Drug Effects Upon Cognitive Performance Under Stress[1]

Paul M. Hurst and Marianna F. Weidner

Institute For Research

The following is an account of the effects of several psycho-active drugs upon cognitive performance in the presence of various stressors. Included are the results of three experiments performed in this laboratory during the past year. A rapidly paced sequential memory task (PSMT) was administered, in addition to various other tests, in all three experiments. The total list of experimental variables included choice of drugs, dosages, incentive conditions, pace of task, storage load demands, and placebo control procedures. The overall purpose was to determine whether certain psychoactive drugs might enhance cognitive performance by non-fatigued subjects, in stressful situations, and what task or situational factors affect the magnitudes of any such drug influences.

THEORETICAL BACKGROUND

The choice of variables was oriented toward the goal of testing a viewpoint (Hurst, 1966) which is, stated briefly:

Drug enhancement of cognitive performance is achieved through mitigation of disturbing influences, rather than through direct facilitation of cognitive processes.

[1]This research was performed on Contract Nonr 4423(00) with the Physiological Psychology Branch of the Office of Naval Research. Dr. Nel Kopp was the medical supervisor, and served as attending physician during the test sessions. The authors wish to thank Dr. H. R. Glenn and his staff at the Pennsylvania State University Health Center for their valuable cooperation in subject screening operations.

Thus, the potentiality of a situation for any drug enhancement should depend upon the extent to which intrinsic or extrinsic task factors tend to degrade performance from that of the optimally motivated subject. Repetitious aspects are thought to induce negative emotional responses ("reactive inhibition," etc.) and thus lead to performance enhancement by psychoanaleptics. Enhancement of cognitive performance by such drugs has not been reliably established in the absence of such factors in normal, non-fatigued subjects (cf. Weiss and Laties, 1962, pp. 18-21, for a review of caffeine and amphetamine effects upon such phenomena.)

When restricted to such boredom-fatigue mitigation, this viewpoint is only a reiteration of that of Barmack (1939). However, it also generates predictions concerning cognitive enhancement in the presence of "emotional" stresses related to anxiety about the task situation. Here, enhancement might be expected with various "ataractic" agents, whose mood-relevant effects would be expected to ameliorate such "emotional" stresses. However, most such agents tend to have negative *direct* effects upon cognitive processes. Enhancement would therefore be expected only within rather narrow dosage ranges, and only in situations where stressful aspects produce marked degradation in non-drugged subjects. Evidence relevant to this hypothesis will now be discussed:

There are many experimental data, which will not be reviewed here, indicating that depressants usually impair task performance in non-disturbed subjects. These results are, in general, unremarkable. Even "tranquilizers," which are sometimes not classed as "depressants," generally manifest some depressive effect if the dosage is large enough

or the experimental design sufficiently sensitive. Of greater interest is the occasional finding, in particular situations, of performance enhancement.

Of the relatively few instances in which enhancement has been reported for such agents, the majority seem to involve use of the drug to allay interfering emotional responses due to some "stressful" aspect of the task or situation. Thus, Hill, Kornetsky, Flanary and Wikler (1952) found that morphine tends to restore reaction times toward normal levels when they have been lengthened by fear of shock. Holliday and Dille (1958) found, with a pointer-pursuit task, that 800 mg. of meprobamate tended to abolish the disruptive effects of anxiety induced by an automobile horn, air blasts, and electric shock (used as punishment for time off target). Interestingly, improvement from meprobamate over the placebo base was noted only on the interspersed "non-punishment" trials, which may of course have been more stressful than those on which punishment actually occurred. Matlin (1964) found that chronic administration of chlordiazepoxide (10 mg. twice daily for two weeks in the guise of vitamins) improved productivity in 64 "retarded" workers who were believed to have been suffering from tensions, instabilities, and neuroses. Unfortunately, no placebo controls were used, although the suggestion effect was presumably reduced by drug administration in the guise of vitamins.

Uhr, Platz, Fox and Miller (1964) observed that a single 1600 mg. dose of meprobamate significantly improved performance on the Michigan Continuous Attention Task, which was administered under stressful conditions (shock trials interspersed with non-shock trials). The interpretation is obscured, in that improvement occurred under non-shock as well

as shock conditions, with the shock x drug interaction being nonsignificant. The authors suggest that a punishment-anticipation effect may have been responsible for the drug's effect on the non-shock trials. (Compare with Holliday and Dille, above, for pointer-pursuit task.) This conclusion is strengthened by previous findings by Townsend (1957) and by Kelly et al (1958) of no significant effects for meprobamate on somewhat similar monitoring tasks performed in the absence of shock stress.

While such perceptual-motor enhancement by CNS depressants is of significance, it is perhaps even more noteworthy that enhancement of cognitive performance has occasionally been elicited by such drugs.

Ritter, Sells, and Mebane (1958) studied the effects of 400 mg. meprobamate, as opposed to 2 mg. pipradrol, 10 mg. methylphenidate, placebo, or no capsule, upon a variety of anxiety and performance indices. They obtained an F-ratio significant at $p<.01$ on the Wechsler digit-symbol substitution test, with all three drug groups markedly excelling the placebo group. They remark, however, that interpretation is impossible because the no capsule group <u>also</u> markedly excelled the placebo group. Interpretation of the results of this powerful ($N=225$) study is subject to the further finding that reported comfort was significantly lower in the no capsule group than in any other. Thus, the placebo effect was negative for performance but positive for comfort. One might infer accordingly that increased anxiety facilitated performance, but this conclusion is at variance with the facilitative effect reported for meprobamate which might be expected to reduce, not increase anxiety.

Burnstein and Dorfman (1959) obtained a reliable 17% reduction in learning time in a complex memory task with 1200 mg. meprobamate. The authors indicate that a relatively high level of anxiety or emotionality

was involved in this situation, due to the high degree of inter-item competition.

Korman, Knopf and Austin (1960) found that serial learning under shock stress conditions was slightly but significantly enhanced by a mild (30 ml.) dose of ethyl alcohol. The results are interpreted as forming an exception to "the dictum of Jellinek and McFarland (1940) that alcohol has a depressing effect on all psychological functions yet measured." Of additional significance, and in accord with the present hypothesis, the control (non-stress) groups showed poorer performance under alcohol. Dimascio (1963) also investigated competitive paired-associate learning (CPAL) under various CNS depressants: phenyltoloxamine, 100 and 200 mg., secobarbital, 50 and 100 mg., and meprobamate, 200 and 400 mg. The college student subjects, who served as their own controls (placebo), required significantly fewer learning trials to reach criterion under the higher doses of meprobamate and phenyltoloxamine, and tended ($p=.10$) to make fewer errors in the process. Paradoxically, the lower dose of phenyltoloxamine significantly ($p<.05$) increased the number of trials to criterion. The "anxiety" or "stress" factor again enters the picture in the form of Taylor MAS scores. These appeared to have no bearing on CPAL under placebo, whereas under 800 mg. meprobamate the subjects with the higher MAS scores significantly ($p<.05$) excelled those with lower MAS scores, both in rapidity of learning and in freedom from errors during the learning process. There was a similar tendency ($p=.10$) under 50 mg. secobarbital or 200 mg. phenyltoloxamine for subjects with the higher TMAS scores to learn the lists with fewer errors than were made by those with lower TMAS scores.

Hughes, Forney, and Gates (1963) used delayed auditory feedback

as a stressor in evaluating effects on a variety of performance tests of alcohol, benzquinamide, or a mixture of the two. They found that the tranquilizer significantly improved performance at reverse reading and "subtraction plus seven." Alcohol quite generally depressed performance. Synergism between the two agents was not evident. Their tranquilizer data support the viewpoint of enhancement through selective interference; their alcohol data do not, and also tend to contradict Korman et al (1960). The difference here may have resulted because (1) different types of stressors were involved, or (2) Hughes et al used 45 ml. alcohol per 150 lb. of body weight, whereas Korman et al used a standard 30 ml. dosage. Certainly, if alcohol is ever to enhance performance, one should expect the dosage level to be critical.

Evans and Smith (1963) measured performance in normal subjects, at a variety of mental tasks, with either 10 mg. *d*-amphetamine sulfate, or 16 mg. morphine sulfate, or both, versus lactose placebo. The tasks, derived from Guilford's "Structure of intellect" model, comprised various tests classified according to the type of mental operation demanded, i.e., Evaluation, Convergent Production, Divergent Production, Memory, and Cognition. Among the many drug effects found, it is most interesting that morphine enhanced the scores of all three tests in the Evaluation category. The authors interpret this finding as follows:

> Guilford has stated that tests in the Evaluation category measure the ability of subjects to make a judgment as to which is the correct response of a limited number of possible alternatives. It may be that tasks of this type which require a 'focusing' or the concentration of attention on task relevant cues will be benefited by the decrease in excitement and distractibility produced by morphine. Calloway and Stone, 1960.

It would appear from these findings that the "depressant" group

operates in a manner quite analogous to the "stimulant" group: performance may at times be enhanced, but only when it would otherwise be degraded below some "normal optimum." For "stimulants," such degradation would presumably have resulted from fatigue or boredom; for "depressants," the degradation would have resulted from emotional stress. It is probable that all of the "depressants" cited above have ataractic, as well as psycholeptic, properties.

In most of the studies cited, the "stress" involved was presumably due to the introduction of some extraneous "stressor" into the task situation; electric shock or delayed auditory feedback. The Evans and Smith data cannot, however, be interpreted in this manner. The only possibility for a "selective interference" interpretation is to assume that the stress was inherent in the tasks themselves. This introduces a whole new class of phenomena which might fruitfully be explored for drug enhancement via "stimulants" and/or "depressants." Certain task parameters--e.g., high input pacing in the presence of certain perceptual and/or decision-making demands--appear to induce a type of stress in the human operator. Many operational tasks involve these parameters. The occurrence of a "dropoff" phenomenon, a sharp decrement in the information transfer rate when input rate exceeds a critical value, has been demonstrated in the laboratory by various investigators, e.g., Alluisi, Muller, and Fitts (1957), Jeantheau (1959), and McKendry and Hurst (unpublished).

Such results are amenable to at least two alternative interpretations:

(1) The decrement is simply a function of input queuing, due to channel-capacity limitations in the organism, which results in the loss of inputs during short-term storage while awaiting processing. Such

a mechanism could produce accelerated decrements even in a computer that was programmed for certain queuing disciplines and storage life-times. This interpretation is derived from the single-channel hypotheses set forth by Hick and Welford (1956), Broadbent (1957a, 1957b), and Welford (1960).

(2) The decrement is caused by "emotional" factors which interfere with the optimal functioning of the human data-processing machine.

It is possible, of course, that both mechanisms are involved. It is also possible that the perceived loss of input data due to (2) could exacerbate the emotional interference, leading to reductions in channel capacity with further input losses, hence increased loss of inputs, increased emotional interference, etc. in a vicious circle.

To the extent that mechanism (1) contributes to the observed decrement, no substantial drug enhancements would be predicted from the selective interference viewpoint. To offset this "queuing" loss would require something like a lowering of disjunctive reaction time, or an increase in short-term storage capacity. Of the two families of stimulants most studied, the amphetamines and the xanthine derivatives, little promise has been shown for increasing short-term storage capacity in non-fatigued subjects (cf. Brengleman, 1958a, 1958b). There is some evidence that amphetamines lower disjunctive RT (cf. Adler, Burkhardt, Ivy and Atkinson, 1950; Kornetsky, 1958), but effects appear to be slight in the absence of fatigue or oxygen deprivation.

Performance decrements resulting from (2) might best be countered by an agent which blocks the interfering emotional responses without impairing the operator's basic ability to perform the requisite data-processing functions. This suggests that "stimulant" or "neutral" agents with mood-active components would be predicted to excel the

typical "ataractic" drugs, which tend to be rather broad-band CNS depressants.

If "depressant" vs. "stimulant" is referenced strictly to the psycholeptic--psychoanaleptic continuum, without prejudice as to component effects upon affective phenomena involving susceptibility to "panic," this prediction might be tested. Design of an adequate test must meet the objection that observed performance enhancement by any "stimulant" drug *could* be attributed to mechanism (1): a direct facilitation of processing ability attributable to psychoanaleptic components, which could occur regardless of any effects mediated by affective phenomena. This objection may be met in two ways:

(1) Relative strengths of various affective components seem to vary among different psychoanaleptic compounds. Thus, it should be possible to vary the "emotional" element independently of psychoanaleptic potency. Interpretation of results would, of course, depend upon confidence with which one could assume true equality of psychoanaleptic components.

(2) Task variables, such as incentive conditions, could be manipulated so as to induce varying emotional responses without changing the basic data-processing requirements.

To implement the first approach, we must establish a basis for assessing relative strengths of "emotional" factors in various psychoanaleptic compounds. Although measurement techniques for such affective phenomena are not highly developed, there are some relevant data:

Certain mood-relevant properties seem to have been established for the amphetamine group. There is some reason to believe that these are of a nature that might block, selectively, the emotional component

of task-induced stress. If we consider the emotional stress factor to be something akin to fear or panic, then a mood effect in the opposite direction might be of benefit. In this respect, the effects of these drugs are ambiguous, but most of the data would lead one to expect *a blocking of task-induced panic*--hereinafter referred to as the "anti-stress" component.

Voluntary expressions of increased confidence, such as the feeling "that it is relatively easy to perform a task," were obtained by Bahnsen, Jacobsen and Thesleff (1938). Increases in relaxation vs. tenseness were observed by Barmack (1939). Decreases in clinical reports of anxiety were obtained by Schilder (1938) and by Korey (1944). A decrease in rated anxiety of a "threatened" group was reported by Lanzetta, Wendt, Langham, and Haefner (1956). Smith and Beecher (1960a) found increases in boldness and self-confidence. Hurst (1962) reported that *d*-amphetamine increased risk-taking in an experimental uncertain-outcome situation, where sizeable risks of a monetary nature were involved. Smith and Beecher (1964) found that 0.2 mg./kg. *dl*-amphetamine increased self-ratings of performance by students taking calculus tests.

On the negative side, Smith and Beecher (1960b) found that 0.2 mg./kg. *dl*-amphetamine induced pessimism with regard to swimming speed in a standard course traversed by trained athletes. This may have been due to a direct effect on estimation of time passage, which tends to be increased by amphetamines (cf. Frankenhauser, 1958; Goldstone, Boardman and Lhamon, 1958). Hauty and Payne (1957) found no significant effect upon level of aspiration scores on the Air Force SAM task. The dosages, however, were small (5 mg. *d*-amphetamine).

Further opposition to the anti-stress notion derives from self-

ratings on such adjectives, by amphetamine subjects, have been reported by Nowlis and Nowlis, 1956; Smith and Beecher, 1960a; and Ross, Krugman, Lyerly and Clyde, 1962. This may, however, be a semantic problem: Increases in "jittery," "clutched up," etc. may be due to sympathomimetic functions which parallel CNS effects of a sharply different direction. Paradoxical results may be produced by shifts in subjects' attention between conflicting cues. Some such postulate seems necessary to explain how the same drug (racemic amphetamine) can increase *anxiety, boldness, and relaxation.*

A directly relevant study was performed by Kenyon and Pronko (1960), who observed the effects of a capsule containing 10 mg. *d*-amphetamine sulfate (versus placebo capsule, versus no capsule) upon performance in a task containing both intrinsic and extrinsic stressor elements. The task required the subjects to read aloud and follow a series of simple statements that directed them to make dial and switch adjustments on a panel before them. A reading pacer provided that intrinsic stressor; extrinsic stressors were delayed auditory feedback and threat of shock. No significant differences in task time or number of panel operations were observed among the three treatment conditions. Noteworthy, also, is that a similar study by Pronko and Kenyon (1959) failed to reveal any consistent differences in performance at this task as a function of 800 mg. meprobamate versus placebo versus no capsule. Yet "stress" was evidently present, since pulse rates averaging over 120 per minute were obtained under all treatment conditions, and performance at this task is normally degraded by the extrinsic stressor (*ibid.*). It is important to note, however, that the performance measures were obtained at time intervals averaging 15 to 25 minutes after ingestion of *d*-amphetamine

(personal communication from G. Y. Kenyon), or 25 to 45 minutes after meprobamate. These may not have been sufficient latencies to register maximum effects from the drugs.

In order to avoid contamination of stress effects with vigilance phenomena, it might be desirable to employ a task of very short duration, as was done by Kenyon and Pronko. An alternative would be to sample behavior at various points in time, in a task of moderate duration. Separate analyses by time intervals should permit separate assessment of drug effects upon phases of the experiment in which varying degress of fatigue/boredom decrement occur in control groups. A factorial design, permitting orthogonal manipulation of drug and stress variables, should permit clear interpretation, in terms of the stress variable, of any drug effects upon performance.

It appeared that these requirements might be met by measuring performance at a paced sequential memory task (PSMT) under varying levels of intrinsic and extrinsic stressors, during various time intervals, and under various psychoanaleptic and/or ataractic drugs. Consequently, the following experiments were performed.

EXPERIMENT I

The first experiment employed four drug treatments: *d*-amphetamine sulfate (Dexedrine), 10 mg.; methylphenidate hydrochloride (Ritalin), 10 mg.; chlordiazepoxide hydrochloride (Librium), 10 mg.; and no active drug.

These medications were postulated to have the following performance-relevant effects: (a) *d*-amphetamine, psychoanaleptic and anti-stress; (b) methylphenidate, psychoanaleptic; (c) chlordiazepoxide, anti-stress; and (d) no drug, none.

Thus, a quasi 2 x 2 factorial combination of psychoactive components was postulated for the four drug conditions. The hypotheses to be tested were drawn from the general viewpoint presented above: that cognitive performance may be facilitated or hampered by a given drug depending on the motivational aspects of the task involved. Thus, when emotional "stress" is low and task duration is prolonged, performance will be facilitated by anti-boredom effects (psychoanaleptics) and not by anti-stress effects. When emotional "stress" is higher and task duration less prolonged, psychoanaleptic components will be relatively less beneficial and anti-stress components more beneficial.

Hypotheses

When stressfulness and exposure time are manipulated independently *in the same task,* the following predictions should hold for performance scores:

H1: *D*-amphetamine groups will excel no-drug groups in performance under both "high stress" and "low stress," and both early and late in the session.

H2: The position of the "anti-stress" groups (chlordiazepoxide and *d*-amphetamine) will improve, relative to methylphenidate or no drug, with increased stress.

H3. As the session progresses, the performance of the "pure psychoanaleptic" (methylphenidate) groups will improve relative to chlordiazepoxide or no drug.

Dependent Variables

<u>The Paced Sequential Memory Task (PSMT)</u>. This is a version of the sequential short-term memory situation extensively studied by Kenneth Lloyd and his colleagues (cf. Lloyd, Reid, and Feallock, 1960, for a detailed description.) Briefly, this is a situation in which the materials to be recalled, and their recall points, are intermixed. A word sequence consists of "member" words (e.g., pine, tin, polo) with "class" words (e.g., tree, metal, sport) interspersed. When a class word is presented, the subject must recall the most recently presented item that belongs to that class (e.g., for "tree" recall "pine," etc.). The average storage load ($\overline{SL}$) can be systematically manipulated, and has been reported to be a good predictor of performance over a range of task variations.

The PSMT employed here involves eight classes, each having nine items. Twelve-item sequences were employed, necessitating some classes to be repeated in each sequence. In other details, the procedure followed that employed by Lloyd et al (e.g., each recall point was identified by a brief 500-cycle tone preceding the class name presentation). The stimuli were presented on a tape recording.

Since the PSMT involves concurrent storage and retrieval operations, it was presumed to have a certain degree of intrinsic stressfulness. Storage load values were chosen within the range (2.8 - 4.8) where performance, according to Lloyd et al (*op cit.*), normally deteriorates rapidly with increasing $\overline{SL}$. Systematic variations in stressfulness were imposed by manipulating incentive conditions.

<u>Mood measures</u>. Mood effects were measured, at intervals, as self-

ratings on the Nowlis Mood Adjective Check List (ACL). The version employed here included eight factors (aggression, anxiety, surgency, concentration, fatigue, social affection, sadness, and egotism) plus two tentative factors (elation and vigor). The postulated anti-stress effect was measured by anxiety (negative) and elation (positive); the psychoanaleptic effect by fatigue (negative) and vigor (positive).

Subjects

Sixty-three Pennsylvania State University students were recruited for a "psychological experiment" by an advertisement offering a chance to earn an average of $10.00. Upon inquiring, the students were told that drugs were involved, and also the names and dosages of the drugs from which their medications would be randomly selected. The general natures of these drugs were explained to them. Only about 10% of those responding to the advertisement declined to participate upon learning about the drug aspect. Another 10% were subsequently excluded because of medical contraindications or the unavailability of clinical records. Thus, it is not likely that the sample represents a population who were unusually eager to participate in a drug experiment *per se*. The sample included both males and females, mainly undergraduate upperclassmen, who were between 21 and 30 years of age (Mdn = 22).

Experimental Design

The experimental design for between-subject comparisons is presented in Table 1. The 2 x 2 x 4 factorial design employs the following variables: incentive (fixed payoff vs. variable payoff), placebo effect (blank capsule before measurements vs. blank capsule after measurements),

and four disguised medications (*d*-amphetamine sulfate vs. methylphenidate HCl vs. chlordiazepoxide HCl vs. no drug). Within-subject comparisons assessed $\overline{SL}$ variations independently of serial effects (linear component), as the three $\overline{SL}$ values were counterbalanced throughout the second PSMT administration. All treatment groups were tested concurrently with a mixed seating arrangement.

The "capsule early" subjects received blank capsules before any measures were taken. The "capsule late" subjects received blank capsules after all measures (except Mood #3) were taken. Hence, a comparison between these groups registers the "placebo" effects on all measures except Mood #3. The drugs were administered in disguised form in <u>all</u> cases (as a "taste perception" experiment); therefore, the drug treatment was completely independent of the "placebo" treatment. This arrangement was suggested by the paradigm of Ross, Krugman, Lyerly, and Clyde (1962), whose design includes the use of "no drug" and "drug disguised" groups in addition to the usual "drug capsule" and "placebo capsule" treatments. Thus, the drug effects and the placebo effects can be separately determined instead of merely estimating a drug's "true" effect by subtracting drug capsule scores from placebo capsule scores. The present arrangement introduces the feature that all groups given drugs receive them in the same, disguised form, regardless of whether or not capsules are given (the capsules being blank). Thus, possible differences attributable to differences in time of ingestion, absorption time, etc., due to a drug being given in solution as opposed to capsule form, are controlled. This modification achieves an orthogonal factorial design with respect to drug and "placebo" (suggestion) effects. One can isolate main effects

Table 1

Experimental Design

(Experiment I)

Incentive	Fixed Payoff								Variable Payoff							
Placebo	Early Capsule				Late Capsule				Early Capsule				Late Capsule			
Drug[1]	D	M	C	ND	D	M	C	ND	D	M	C	ND	D	M	C	ND
No. of Subjects	4	4	4	4	4	4	4	4	4	3	4	4	4	4	4	4

[1]Legend: D = *d*-amphetamine sulfate, 10 mg.

M = methylphenidate HCl, 10 mg.

C = chlordiazepoxide HCl, 10 mg.

ND = no drug

for drug and placebo conditions and also separate "placebo effect" for each drug or no-drug condition, depending on whether the disguised medication was preceded by administration of a blank capsule. These separate "placebo effects" will not be identical if there is any interaction between true drug effects and the "placebo effect" factor.

Procedure

The single experimental session commenced at 1:00 p.m. and lasted four hours. The exact time of each event in the experiment is indicated in Table 2.

The subjects had been told to eat "normally" during the preceding 24 hours.

Each subject drew a numbered card from a shuffled deck that had been placed in a bag. The number, which determined his seating position and treatment group, was recorded by the physician in charge who was the only person who knew the drug assignments by subject names until after the scoring was completed. The seat numbers included in each treatment group were spread over the room in approximate spatial balance, so that the members of each group were widely dispersed.

Instructions. The following excerpt from the initial instructions is reproduced here, since it is crucial to the interpretation of the effects of the "placebo" variable.

"You are here to participate in an experiment to determine the effects of stimulants and tranquilizers on perception, mood, alertness, and ability to concentrate. I don't know which drugs will help or hurt

Table 2

Activity Schedule (Experiment I)

Activity	Time (in minutes)
First Capsule Administration and Perception Test	*$t_i - 35$
Drug Ingestion and First Mood ACL	t_i
Test Instructions	$t_i + 20$
First Performance Test	$t_i + 40$
Payoff Instructions	$t_i + 75$
Second Mood ACL	$t_i + 85$
Second Performance Test	$t_i + 95$
Second Capsule Administration	$t_i + 150$
Third Mood ACL	$t_i + 175$
Dismissal	$t_i + 180$

*t_i = time of ingestion

you most in the payoff task.

If you have been assigned to a fixed payoff group, you will receive $10.00 for participation in this experiment. If you have been assigned to a variable payoff group, your payment will average $10.00 but may range from $5.00 to $15.00, depending upon your performance in the data processing (sequential memory) task. Details of the payoff arrangement will be explained later. I want to emphasize, now, that in no case will the results of the perception experiment or the mood checklists have any influence on your payment.

Now, read the card on the back of your clipboard. This tells you whether you are to be given the fixed or the variable payoff and whether you are to take the drug early or late. Everyone here today will be given a drug, one of the three. The only difference will be which drug of the three, and when it is given.

Now, Dr. Kopp will give you your drug. Please do not swallow it until she tells you to do so."

<u>First capsule administration (1:15 p.m.).</u> The attending physician, who had been identified to the subjects, passed out blank capsules to the "drug early" groups, taking them from three cryptically labelled bottles while consulting an "assignment chart." When the subjects had taken their capsules, the forthcoming taste perception test was explained to them.

<u>Perception test (1:15 p.m. to 1:55 p.m.).</u> The test was used primarily as a cover for disguised drug administration. Secondarily, it served to indicate how successfully the drug tastes had been disguised. The instructions were as follows:

"You have been given three portions of decaffeinated instant coffee, to which varying amounts of different coffee-flavoring agents have been added. It is known that the drugs which some of you have taken alter taste perceptions for sweetness and bitterness. This effect comes on before the mood effect, which in turn precedes the performance effect. We wish to correlate these taste phenomena with the other effects to be observed later. The flavoring agents are designed to vary the sweetness and bitterness of the three cups of coffee. I want you to rank the three cups in order of sweetness, and also in order of bitterness, putting the rank assigned to the cup opposite the letter designating it. If cup B is sweetest, write 1 after the letter B under the sweetness heading, then write the numeral 2 beside the second sweetest, etc. Then use this ranking procedure with the bitterness scale. I would like you also to assign a number rating to each cup corresponding to its degree of sweetness or of bitterness, using a scale of zero to ten. Thus, for the "sweetness" scale, zero means no perceived sweetness, ten means it is as sweet a cup of coffee as you have ever tasted, and the intermediate steps represent equal-appearing intervals in between. Let number 5 represent what you would expect from an ordinary cup of coffee with one teaspoon of sugar."

The subjects were then instructed on the order in which the cups were to be drunk, that the contents of each cup (about 120 cc.) were to be drunk completely, with mouth-rinsing in between cups, and that they were to complete the entire process in 10 minutes "for us to meet our timetable."

Every subject had been provided with three paper cups, to which a total of 10 cc. powdered decaffeinated coffee had been added, in

addition to 50 cc. Borden's Cremora, 10 cc. confectioner's sugar, and (for the drug groups) 10 mg. of the appropriate drug. Each subject assigned to a drug treatment received the drug, divided among the three cups, in powdered form. Water at 60° C. was provided to make the potion pleasantly hot but quickly drinkable. The flavoring additives were necessary because one of the drugs, chlordiazepoxide HCl, has a bitter taste that requires strong masking. An additional problem is that this drug undergoes denaturation to a therapeutically significant degree when kept in aqueous solution for much more than ten minutes. Thus, the potions could not be premixed in liquid form and had to be drunk within ten minutes after the water was added. This timetable was met successfully: All drugs were ingested between 1:45 and 1:55. (The approximate median time of ingestion, 1:50, will be hereafter referred to as "t_i.")

First Mood ACL (t_i to t_i + 15). Immediately after ingestion of the liquids, the subjects were instructed to fill out the first Nowlis Mood ACL. It was completed by all subjects less than 20 minutes after ingestion of the drug-containing liquids. Thus, it was not expected to reflect drug effects, and was included mainly as a time filler.

Test instructions (t_i + 20 to t_i + 40). Immediately following the first mood measurement, instructions were given for the sequential memory task. Lists of the item and class names were given to the subjects for examination, then returned.

First performance test (t_i + 40 to t_i + 65). All subjects recorded their answers to a 25-minute version of the sequential memory task which was composed of 18 word sequences, each consisting of 12 items with

12 interspersed recall points. This "practice" tape employed the same class names as the "payoff" tape, but with different selections of items and different locations of recall points. The $\overline{SL}$ values of the word sequences were in a low-medium-high order.

Payoff instructions ($t_i + 75$ to $t_i + 85$). Following a ten minute break, during which they were allowed to smoke, the subjects were given a description of the payment arrangement for the forthcoming "payoff session."

Members of the "fixed payoff" group would each receive $10.00 for participation, regardless of performance. Members of the "variable payoff" group would receive an average of $10.00 each but the payment would vary from $5.00 to $15.00 in ten equal steps, with approximately equal numbers of subjects in each bracket.

Second Mood ACL ($t_i + 85$ to $t_i + 90$). The second ACL was given at this time in an attempt to catch the peaks of any mood effects. Of the postulated two components to be measured, the mood-related one was expected to "peak out" earlier than the psychoanaleptic one.

Second performance test ($t_i + 95$ to $t_i + 145$). This involved a 50-minute tape with a total of 36 sequences, 12 for each $\overline{SL}$ value, which were counterbalanced to permit resolution of $\overline{SL}$ effects from serial effects.

Second capsule administration ($t_i + 150$). The subjects were instructed:

"Now, Dr. Kopp will administer the drugs to the "drug late" groups. There will be no more performance tests, but we wish to compare mood effects for drugs given after exposure to a stressful task with those

of drugs given before the task. Please do not swallow your capsule until she tells you to do so."

The attending physician, using the same procedure as before, gave identical blank capsules from the three bottles to all members of the "drug late" groups. The primary reason for the second capsule administration was to reconcile ethics with secrecy concerning the experimental design. Each subject who had received a drug should know that he had received one, before leaving the experiment. Otherwise, the admonitions against operating dangerous machinery or alcoholic overindulgence might not be heeded. Yet half of those receiving drugs in the coffee had as yet received no capsules, and presumably believed they had received no drug. The alternative of telling them that they had received a drug in the coffee would have jeopardized any future use of the drug disguised technique with the local subject populations.

Third Mood ACL and comments (t_1 + 175 to t_1 + 180). After a 20 minute break "to allow the drugs to take effect" the third ACL was filled out by all subjects. To ascertain whether the deception was successful concerning the mode of drug administration, the subjects were invited to write their comments on the experiment on the back of the ACL form.

Results

In the tabular material to follow, all significance levels refer to results of analysis of variance in a between groups, fixed constants 2 x 2 x 4 factorial model. Where paired comparisons are involved,

2-tailed results are always reported (for consistency of format), even though the directionality was predicted for some cases.

Perception test. A significant difference in "bitterness" ($p<.05$) was obtained for chlordiazepoxide vs. no drug, whose mean ratings were 4.63 and 3.33, respectively. No significant difference was found when these two conditions were compared for "sweetness," nor were any significant differences found in sweetness or bitterness for any other drug-drug or drug-no drug comparison. Thus, the masking seems to have been entirely successful with *d*-amphetamine and methylphenidate, but not with chlordiazepoxide, with which it might be considered largely successful. Recalling that the bitterness scale ranged from 0 (least bitter coffee ever tasted) to 10 (most bitter coffee ever tasted), a rating of 4.63 should be well within the subject's range of experience with "bona fide" coffee.

First performance test. Only the drug variable yielded a reliable main effect. This was significant at $p<.05$ for the test total and for the first half of the test, but not for the second half. Significance of the F-ratios must be attributed largely to the superiority of *d*-amphetamine groups. No other drug condition was reliably superior to no drug. (See Table 3)

The general decline in performance during the second half (52-64 minutes post-ingestion) must be attributed partially to increased $\overline{SL}$, since the first performance test did not counterbalance load for serial effects. However, the similar decline in the second period of the second test, which was counterbalanced, suggests additional factors

Table 3

Mean PSMT Total Scores, Differences[1]

and "t" Values for First Test

(Experiment I)

	Mean	D	M	C	ND
d-amphetamine	63.45%		2.07*	2.89***	2.66**
Methylphenidate	57.18%	6.27		0.77	0.56
Chlordiazepoxide	54.83%	8.62	2.35		0.22
No Drug	55.50%	7.95	1.68	-0.67	

*p<.05

**p<.02

***p<.01

[1]Differences are column means minus row means.

such as proactive inhibition.

D-amphetamine produced significantly higher scores ($p<.05$) than its nearest competitor in the first half. In the second half, it was significantly superior to chlordiazepoxide and no drug, but not to methylphenidate. In total score, *d*-amphetamine was superior to methylphenidate ($p<.05$), chlordiazepoxide ($p<.01$), and no drug ($p<.02$).

A significant interaction ($p<.05$) was found between drug and incentive during the second half of this test. This was due almost entirely to a negative incentive effect under no drug (superiority of fixed payoff, or low "stress") to variable payoff with absence of consistent incentive effects in any of the drug conditions).

Significant interactions were also found for incentive x placebo effects in each half of the test separately ($p<.05$, $p<.05$) and in the test total ($p<.025$). The fixed payoff groups performed better with placebo effect absent, and the variable payoff groups performed better with it present. The significant interactions involving the "incentive" condition were quite unexpected, since all subjects had been informed that payoff would not depend on performance in this first test. There may have been increased anxiety on the part of "variable payoff" subjects due to knowledge that their payments would be determined by a subsequent administration of this demanding task.

<u>Second performance test</u>. No significant F-ratio was obtained for the "drug effect" variable. Separate paired comparisons were nevertheless made to test prior hypotheses about the drugs involved. *D*-amphetamine excelled each other drug condition at $p<.05$ in the second 12-minute quarter. When total scores were compared, only the positive *d*-amphetamine-chlordiazepoxide difference was significant. Thus, during the

second test *d*-amphetamine generally lost its statistical superiority over the other drug conditions. The differences in means, however, continued generally to favor this drug by a 4.69% to 6.79% margin. (See Table 4.)

The placebo factor was significant at $p<.05$, in the direction of "negative placebo effect," during the first quarter. This effect faded during the remainder of the test and was not significant for total performance. No other main effect or interaction was significant, although the interaction between incentive and placebo effects at times approached significance and maintained the direction previously reported. (See Table 5.) The main effect of the incentive condition was always very small and never approached significance. The variations in $\overline{SL}$ led to sizeable differences in mean performance, but failed to moderate drug effects upon performance. (The superiority of *d*-amphetamine to no drug was 4.3% for low $\overline{SL}$, 5.6% for medium $\overline{SL}$, and 4.8% for high $\overline{SL}$.)

The overall course of performance effects during the two tests is plotted on a continuous time axis in Figures 1, 2 and 3. Figure 1 depicts the time course by each drug condition, summarized over variations in the incentive and placebo conditions. Figures 2 and 3 depict drug-performance curves separately for fixed payoff (low "stress") and variable payoff (high "stress"). Note that both *d*-amphetamine and chlordiazepoxide yielded relatively better results early in the session, and that *virtually all of d-amphetamine's overall superiority derived from the "high stress" condition.*

Table 4

Mean PSMT Total Scores, Differences[1]

and "t" Values for Second Test

(Experiment I)

	Mean	D	M	C	ND
d-amphetamine	69.33%		1.49	2.19*	1.58
Methylphenidate	64.64%	4.69		0.67	0.07
Chlordiazepoxide	62.54%	6.79	2.10		-0.61
No Drug	64.44%	4.89	0.20	-1.90	

*p<.05

[1]Differences are column means minus row means.

Table 5

Performance Means (Total Per Cent Correct), Incentive x "Placebo Effect"

(Experiment I)

(Data combined from all drug conditions)

First Test*

	With Capsule	Without Capsule	Mean
Variable Payoff	58.68%	55.47%	57.07%
Fixed Payoff	54.77%	62.04%	58.41%
Mean	56.73%	58.75%	57.74%

*Incentive x placebo effect interaction significant at $p<.025$.

Second Test

	With Capsule	Without Capsule	Mean
Variable Payoff	66.35%	65.87%	66.11%
Fixed Payoff	61.18%	67.55%	64.37%
Mean	63.77%	66.71%	65.24%

<u>First mood scale</u>. A significant drug effect upon "egotism" was indicated, with methylphenidate exceeding "no drug" and every other drug condition, at $p<.05$. This result seems improbable in view of the first mood scale having been completed within 20 minutes after ingestion of the active compounds. The "elation" scale revealed a significant ($p<.01$) interaction between drug and incentive, with the incentive effect being positive for "no drug" but negative for all active drugs. Again, a rational interpretation is difficult.

A significant placebo effect ($p<.05$) was found upon "fatigue," in a positive direction. No significant main effects was obtained for incentive.

<u>Second mood scale</u>. Significant F-ratios were obtained for drug effects upon "fatigue" ($p<.01$) and "vigor" ($p<.01$). These were mostly accounted for by decreased fatigue and increased vigor for the *d*-amphetamine conditions. On the "fatigue" factor, *d*-amphetamine groups reported scores that were significantly lower than no drug ($p<.001$) or chlordiazepoxide ($p<.01$), but not significantly lower than methylphenidate. For "vigor," *d*-amphetamine exceeded no drug ($p<.005$), chlordiazepoxide ($p<.005$), and methylphenidate ($p<.05$). No other drug comparison was significant.

The placebo effect upon "fatigue" was again obtained in the positive direction, at $p<.05$.

The incentive variable had a significant effect only upon "anxiety," but this was very strong ($p<.001$) and in the direction of greater anxiety for the variable payoff groups. *This suggests that the*

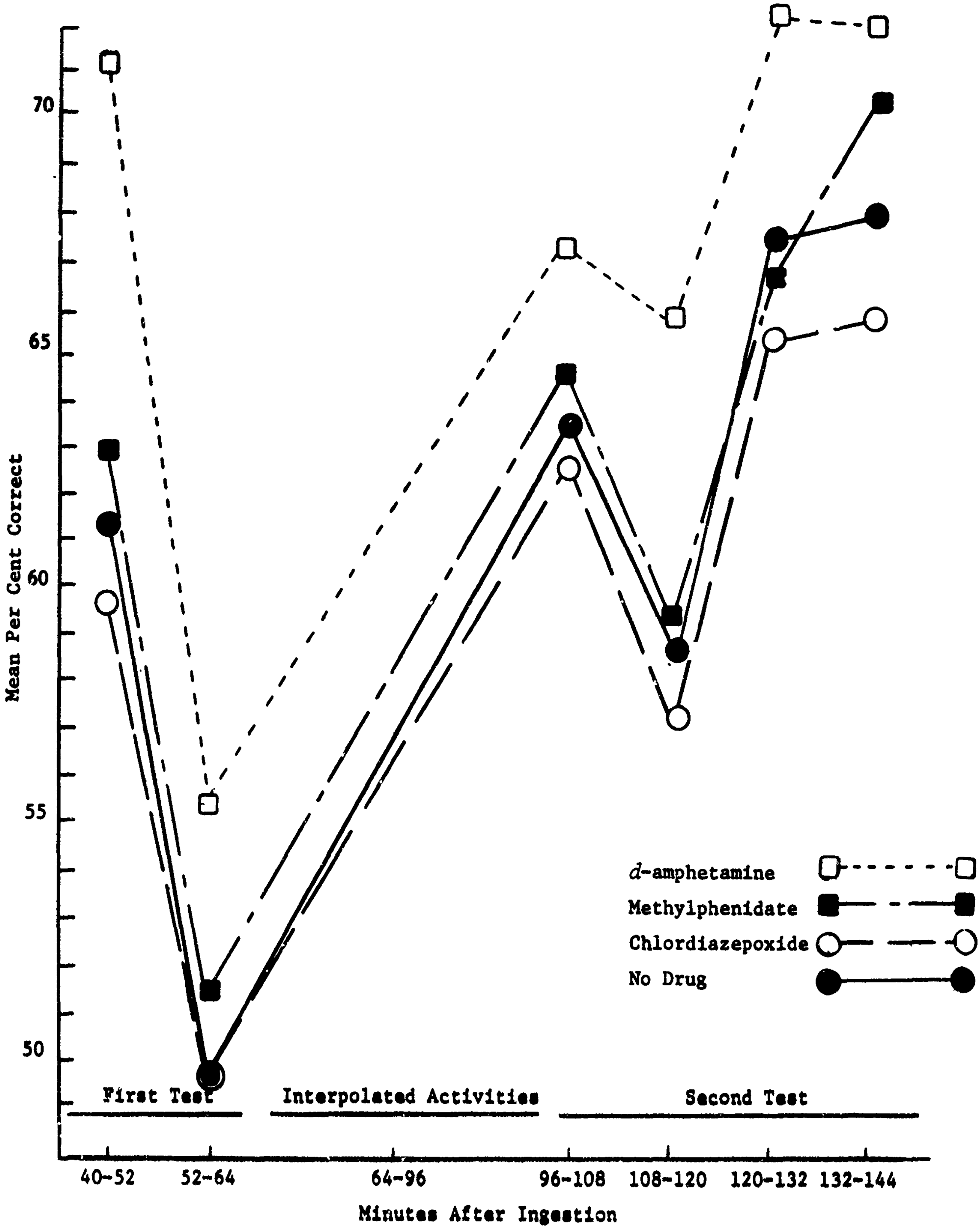

Fig. 1. Performance vs. Time After Drug Ingestion, PSMT Total Scores

(Experiment I)

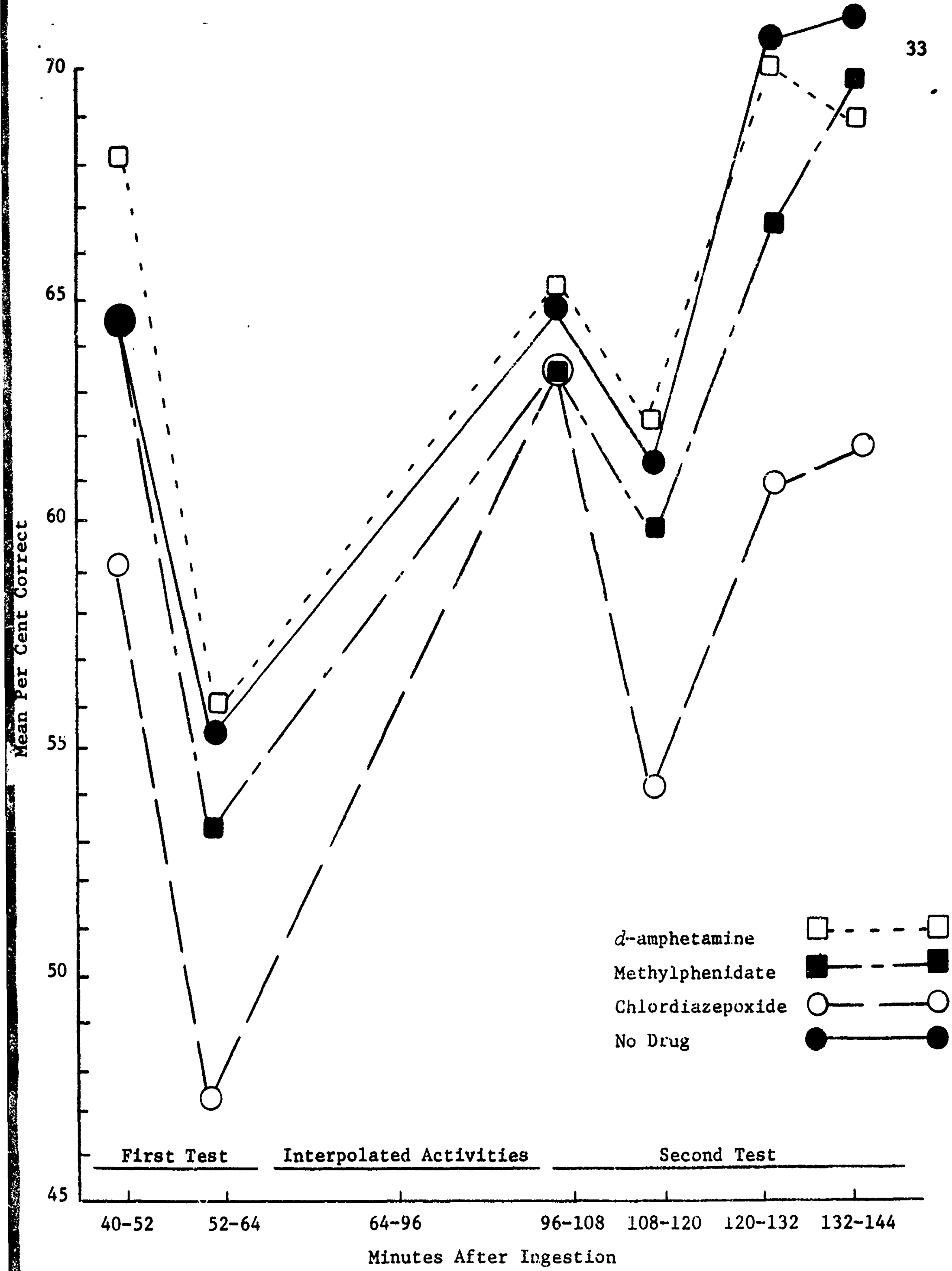

Fig. 2. PSMT Performance vs. Time After Drug Ingestion, Low Stress Condition

(Experiment I)

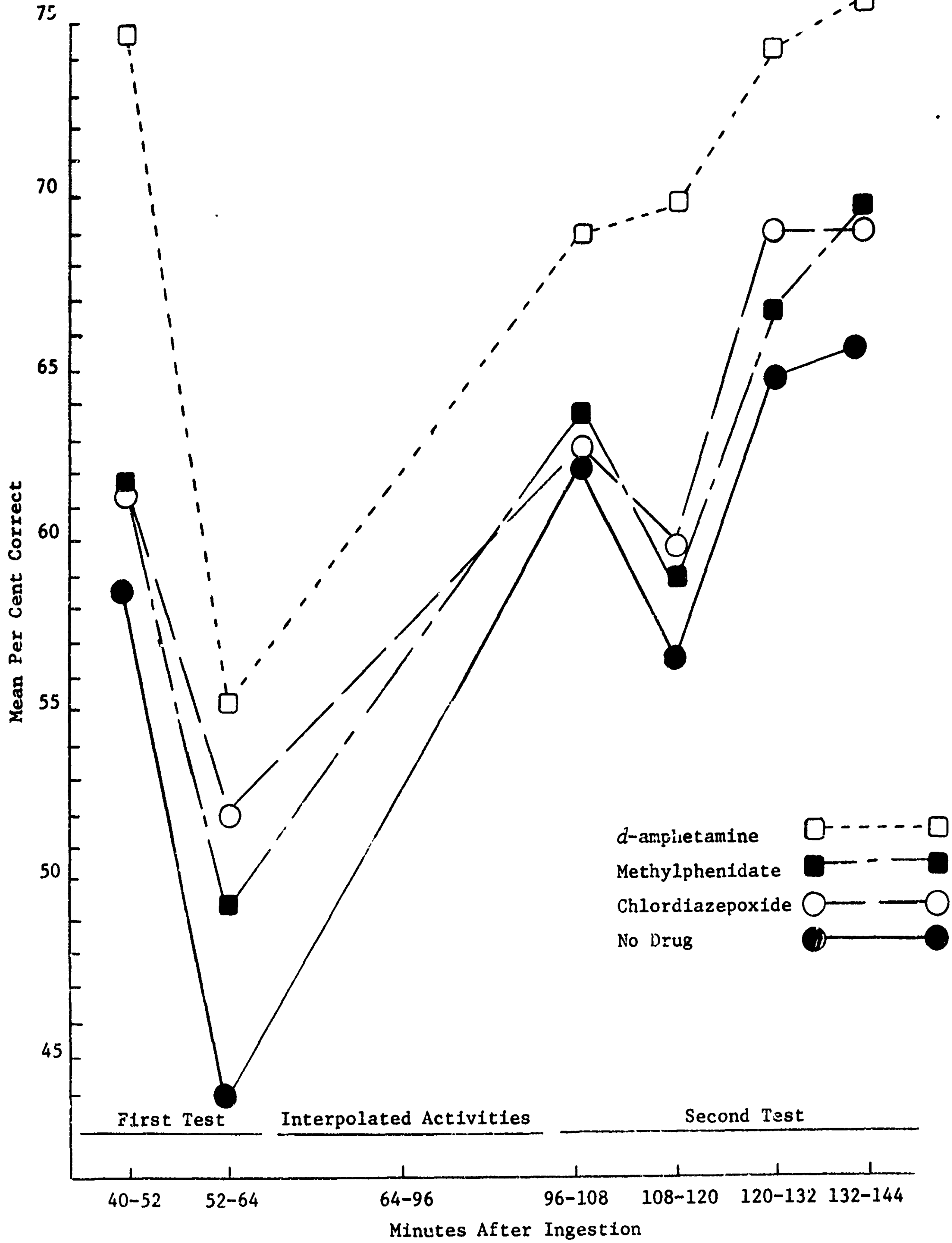

Fig. 3. FSMT Performance vs. Time After Drug Ingestion, High Stress Condition

(Experiment I)

incentive variation did indeed cause differences in "stressfulness" of the test situation, recalling that the second mood scale was interposed between initial exposure to the task and the "payoff" test.

Third mood scale. No significant drug effects or interactions involving them were obtained. The only effects of significance involved incentive x placebo effect interactions, which were significant for "surgency" ($p<.05$) and "elation" ($p<.01$). The placebo effect here was the differential effect of having just received the capsule 20 minutes before, or having received it at the start of the experiment. The "late capsule" groups who had competed for variable payoff were higher in "surgency" and "elation" than the corresponding early capsule groups, but the late capsule groups assigned to fixed payoff were lower in these mood factors than the corresponding early capsule groups. No rational interpretation can be advanced for these findings.

Subjects' comments. One subject indicated, by unsolicited personal comment to Dr. Kopp during the experiment, that he thought the drugs were in the coffee. Further indications of this suspicion did not appear in the optional written comments received from 55 of the 63 subjects.

Discussion

H1: *D*-amphetamine groups will excel no-drug groups in performance under both "high stress" and "low stress," and both early and late in testing.

Support to this hypothesis derives from the consistent superiority

of the *d*-amphetamine groups throughout both performance tests, although the superiority failed to reach statistical significance during the greater part of the second test. The "fading" was quite unexpected, particularly in view of the widespread belief that amphetamines are most effective (or <u>only</u> effective) when performance has been degraded by fatigue, monotony, etc. It suggests that, of the postulated two psychoactive components for this drug, the anti-stress factor was the more important in this situation. Tentatively supporting this interpretation is the much greater margin of superiority for *d*-amphetamine under "high stress" (variable payoff) than under "low stress" (fixed payoff), as revealed in Figures 2 and 3. The tentative conclusion was that exposure to the PSMT has a stress-provoking effect which tends to "adapt out" with practice under either incentive conditions. This question, and the underlying hypothesis, could be tested by imposing incentive variations at the initial exposure to the PSMT. (See Experiments II and III.)

H2: Increased stress will improve the performance of chlordiazepoxide and *d*-amphetamine groups relative to methylphenidate or no drug.

This hypothesis was not reliably confirmed, in that the incentive x drug effect interaction did not reach statistical significance. However, the results are in the predicted direction:

Chlordiazepoxide groups averaged 10% better performance under "high stress" than under "low stress," and *d*-amphetamine groups averaged 9% better in a similar comparison; no drug groups performed 7% worse under "high stress," and methylphenidate groups very slightly worse (1%) under "high stress."

H3: Lengthened exposure to the test task will improve the performance of methylphenidate groups relative to chlordiazepoxide or no drug.

Again, the results are in the predicted direction (See Figure 1), but the hypothesis is not confirmed since none of the differences between the methylphenidate, chlordiazepoxide and no-drug conditions was statistically significant during either of the tests.

Mood effects. While *d*-amphetamine yielded significantly higher scores for "vigor" and lower scores for "fatigue," it did not reduce "anxiety." The effect on this factor, while non-significant, was in the opposite direction. This is in accord with the published data and may, as previously suggested, result from sympathomimetic components which could outweigh any increases in assurance, self-confidence, etc. that may be produced by these drugs. Further investigation of these factors is needed to resolve the various factors evidently involved in drug effects upon reported "anxiety," "fear," "confidence," "boldness," etc. One possibility is to incorporate a "boldness" scale for comparison with the "anxiety" scale. (See Experiments II and III.)

Failure of either methylphenidate or chlordiazepoxide to register a significant mood effect, when compared with no-drug, suggests that either mood-related components were weak or that the dosages were too small. In the case of chlordiazepoxide, the latter alternative may well prove correct. There appears to be an unusually wide range of individual differences in thresholds to this drug's effects. Thus, while one chlordiazepoxide subject fell asleep during the second performance test (because of the drug?), the dosage may nevertheless

have been generally inadequate. Decisive evaluation of such drugs would require tailoring the dosages to individual tolerances established by a series of pretests.

Summary of Experiment I

An experiment was performed to test the interaction between drug/placebo effects and incentive conditions in a "task-induced stress" framework. Its purpose was to test hypotheses concerning the relative roles of "psychoanaleptic" and "anti-stress" components in the drugs involved.

Sixty-three student volunteers were administered either *d*-amphetamine sulfate (10 mg.), methylphenidate HCl (10 mg.), chlordiazepoxide HCl (10 mg.), or no drug. Half of each group received a capsule (placebo effect) and half did not. In all cases, the drug was disguised in decaffeinated coffee given under the cover of a "taste perception test."

Self-ratings of mood were obtained with the Nowlis Adjective Check List. Performance scores were obtained from two tests with a forced-pace sequential memory task (PSMT). During the second test, motivation or "stress" was manipulated by requiring half of each drug/placebo group to work for a fixed payoff and half for an incentive payoff based upon performance.

Significant mood effects were generally limited to changes in "fatigue" and "vigor," attributable chiefly to the energizing effect of *d*-amphetamine. In the PSMT, superior performance was obtained from *d*-amphetamine groups relative to the other drug and no drug groups. This superiority was significant at $p<.025$ during the first test,

but declined progressively, and failed to reach statistical significance during most of the second test. The margin of superiority of *d*-amphetamine over methylphenidate or no drug was considerably greater under "high stress" than under "low stress."

The incentive and placebo effect variations were generally inconclusive, although there was a tendency for *d*-amphetamine and chlordiazepoxide groups to do relatively better in the "high stress" conditions. Virtually all of *d*-amphetamine's mean advantage was contributed by groups assigned to the "high stress" condition.

Since the superiority of *d*-amphetamine was greater (1) under high stress and (2) during the earlier stages of testing, the results lent some support to the postulate of an "anti-stress" component for this drug. They tended to contradict the viewpoint that cognitive performance enhancement by amphetamines is dependent upon the prior existence of fatigue or boredom.

EXPERIMENT II

This study was designed to (1) verify the apparent PSMT enhancement produced by *d*-amphetamine in Experiment I, (2) determine whether such enhancement is, indeed, positively related to stress levels, and (3) explore the possibility that cognitive performance under stress might be further improved by adding secobarbital or chlordiazepoxide to the *d*-amphetamine dosage employed in Experiment I.

Some CNS effects of barbiturates seem to be diametrically opposed to those of the amphetamines. Yet, mixtures of amphetamines and barbiturates have been observed to show synergism with respect to other effects, such as exploratory behavior in rats (Rushton and Steinberg,

1963a, 1963b). Laties (1961) reported enhancement of perceptual-motor performance in humans from an amphetamine-secobarbital combination. Whether such phenomena are attributable to physiological additivity of component effects is debatable. Rushton and Steinberg obtained more than additive activity increases, dosage for dosage with mixtures of amphetamines and amobarbital. This suggests true potentiation if we can assume equality of units of measurement. The *d*-amphetamine-chlordiazepoxide combination has been little investigated with human subjects under experimental conditions. It was included for comparison with the *d*-amphetamine-secobarbital combination to explore the possibility that 10 mg. of chlordiazepoxide could bolster the "anti-stress" component with less degradation of the basic cognitive abilities involved in the memory task.

The drug conditions to be compared were:

D = *d*-amphetamine sulfate, 10 mg.

D + S = *d*-amphetamine sulfate, 10 mg. + sodium secobarbital, 50 mg.

D + C = *d*-amphetamine sulfate, 10 mg. + chlordiazepoxide HCl, 10 mg.

ND = no drug

Each of the above drug conditions occurred with and without a preceding capsule, all drugs being administered in disguised form. Two levels of stress (low = fixed payoff, high = variable payoff) completed the three-factor layout.

Hypotheses

PSMT Performance

H1: The effects of D will excel ND under both "high stress"

(incentive payoff) and "low stress" (fixed payoff), both early and late in the test session.

H2: The effects of D + S or D + C, relative to D or ND, will be more beneficial under "high stress" than under "low stress."

H3: The effects of D + S or D + C, relative to D or ND, will be more beneficial in the earlier phases of the sequential memory test session.

Judgment

H4: Relative to actual performance, self-rated PSMT performance will be most favorable with D + S and D + C, not so favorable with D, and least favorable with ND.

Apparent Time Duration

H5: The apparent duration of a given time interval will be lengthened by *d*-amphetamine. (The effects of the combination treatments are not predictable.)

H4 and H5 are not derivable from the present viewpoint, but involve relevant findings reported by others.

Dependent Variables

The 48-minute version of the PSMT employed in the second test of Experiment I was used here. The augmented short form of the Nowlis MACL was also employed again, with the addition of a postulated "boldness" factor. The coffee-tasting test was used, as in Experiment I, to permit disguised administration of the active medications. A time perception test and a performance self-judgment exercise were added to the Experiment I package. Descriptions of these follow:

Time Perception

Reports of Goldstone, Boardman, Lhamon (1958), and Frankenhaeuser (1958) indicate that amphetamines cause individuals to overestimate the length of a time period while barbiturates cause them to underestimate the length. This result bears upon the findings of Smith and Beecher (1960b), regarding estimates of swimmers of time taken to traverse a fixed course under amphetamine vs. placebo or secobarbital: Was this effect due to pessimism or to distorted time perception *per se*?

The task consists of thirty 1000-cycle tones which vary in 0.1 second increments, from 0.5 second to 1.5 seconds, without any 1.0 second periods. Each period is accurate to ±0.02 seconds. Each of the ten possible tone periods is repeated three times and the thirty periods are presented in a randomized sequence. As the tape-recording is played, each subject indicates his estimate on the response sheet by checking either the "shorter than a second" category or the "longer than a second" category.

Performance Judgment

In order to obtain data germane to the report by Smith and Beecher (1964) that amphetamines cause an individual to overestimate certain intellectual accomplishments, each subject in the second session of this experiment was asked, upon completion of the PSMT, to estimate the percentage of items he had correctly answered.

Subjects

One hundred thirty-six students at The Pennsylvania State University, undergraduates and graduates, served as volunteer subjects. The group

was composed of 92 men and 45 women whose median ages were 22.1 and 21.8 years, respectively. None had participated in Experiment I. They were recruited through an advertisement in the university newspaper, requesting subjects over 21 for a psychological experiment. As before, the advertisement did not mention drugs. However, volunteers were given a list of 13 drugs "from which your medication will be selected." This included dosages (alone and in combination) of various barbiturates, minor tranquilizers, stimulants and an anti-motion sickness compound. They were urged to examine the list and, if in doubt, to consult with family physicians before committing themselves to participate. As before, their university health records and physical examination data were used by Dr. Kopp to screen out those with medical contraindications.

Experimental Design

The experimental design was a 2 x 2 x 4 factorial with the following variables: incentive (fixed payoff vs. variable payoff), placebo effect (blank capsule before performance test vs. blank capsule after performance test) and four medications (D vs. D + S vs. D + C vs. ND).

To vary the degree of stress resulting from the short-term memory task, subjects were paid for their participation in two different ways. Half the group received $12.00 regardless of their scores on the PSMT (Fixed payoff). Members of the other half whose scores on the PSMT were in the high-scoring half of this group received $20.00; those whose scores were in the low-scoring half, $5.00 (variable payoff). Thus, payoff range was higher and variance much higher than with the

incremental scheme employed in Experiment I.

As before, half of each incentive group received a blank capsule before any of the measurements were taken. The other half received a blank capsule after all measurements except the third MACL. Each incentive x placebo subgroup was further subdivided according to the medications actually administered in the coffee. Thus, the basic design of Experiment I was repeated, except for the selection of drugs. (Refer to Table 6.)

Procedure

The experiment was conducted in two sessions, spaced four days apart. Treatment conditions were balanced within each session. Sixty-seven subjects attended the first session; sixty-nine, the second session. Each session was convened at 6:15 p.m. Subjects were instructed to eat normally.

Subject numbers corresponding to the various treatment level combinations were assigned randomly to the seats prior to the experiment. Upon entering the experimental room, subjects were instructed: "Sit in any seat where there is a clipboard, but do not disturb the materials." The clipboards were placed face down to prevent responding to number preferences.

The activity schedule for both sessions are presented in Table 7. Included in the table are the post-ingestion times (in minutes) during which the various measures were taken.

Table 6

Experimental Design

(Experiment II)

Incentive	Fixed Payoff								Variable Payoff							
Placebo	Early Capsule				Late Capsule				Early Capsule				Late Capsule			
Drug[1]	D	D+S	D+C	ND	D	D+S	D+C	ND	D	D+S	D+C	ND	D	D+S	D+C	ND
No. of Subjects	8	8	8	10	8	8	8	10	8	8	8	10	8	8	8	10

[1] Legend: D = *d*-amphetamine, 10 mg.

D+S = *d*-amphetamine, 10 mg. + secobarbital, 50 mg.

D+C = *d*-amphetamine, 10 mg. + chlordiazepoxide, 10 mg.

ND = no drug

Table 7

Activity Schedule (Experiment II)

Activity	Time (in minutes)
Convene, introductory remarks	$*t_i - 64$ to $t_i - 29$
Capsules to "drug early" subjects	$t_i - 25$ to $t_i - 22$
Perception Experiment I (taste) (actual drug ingestion)	$t_i - 06$ to $t_i + 07$
Perception Experiment II-A (time)	$t_i + 14$ to $t_i + 19$
PSMT Instructions	$t_i + 19$ to $t_i + 29$
Ten-minute break	$t_i + 29$ to $t_i + 41$
MACL (#1)	$t_i + 45$ to $t_i + 48$
PSMT - Further Instructions	$t_i + 50$ to $t_i + 66$
PSMT	$t_i + 66$ to $t_i + 116$
Ten-minute break	$t_i + 118$ to $t_i + 128$
Perception Experiment II-B (time)	$t_i + 131$ to $t_i + 136$
MACL (#2)	$t_i + 140$ to $t_i + 143$
Capsules to "drug late" subjects	$t_i + 147$ to $t_i + 150$
MACL (#3)	$t_i + 165$ to $t_i + 168$

$*t_i$ = time of ingestion

Results

Sequential Memory Task Performance

Regardless of $\overline{SL}$, no reliable performance effects were obtained for drugs, incentive, or placebo conditions. The performance means were in the predicted direction, with *d*-amphetamine either alone (D) or in mixture (D + S or D + C) exceeding the no-drug condition. However, these differences were small (none greater than 4%) and not significant. (See Table 8.) Nor was there any reliable indication that any drug effects might be dependent upon "stress" levels, although the D and D + C results were somewhat more favorable under "high stress" (variable payoff). There was likewise no confirmation of the earlier suggestion that performance effects from *d*-amphetamine were stronger early in the test sequence. This time, the performance curves were largely parallel. (See Figures 4, 5, and 6.)

A significant ($p<.05$) day effect was obtained for PSMT totals, in favor of the first session. It is noteworthy that the second session ran into the final exam period for these students.

Judgment of Performance

Subjects in general tended to underestimate their performance levels in the sequential memory task. There was no reliable drug or incentive effect upon this bias, although D groups manifested a somewhat stronger tendency to *underestimate* than did any of the other groups including ND. (See Table 9.)

Table 8

Paced Sequential Memory Task: Main Effects Means[1]

(Experiment II)

Division or Condition	Fixed Payoff	Variable Payoff	"Drug Early"	"Drug Late"	*d*-amphetamine	*d*-amphetamine + Secobarbital	*d*-amphetamine + Chlor-diazepoxide	No Drug
First Quarter	52.30	54.66	54.87	52.08	51.59	54.43	54.92	53.08
Second Quarter	53.04	55.34	55.15	53.23	53.39	55.32	54.95	53.31
Third Quarter	62.06	64.98	64.57	62.47	63.05	64.29	65.05	62.06
Fourth Quarter	64.04	65.25	65.47	63.82	64.76	65.71	65.77	62.80
Low Difficulty	75.40	76.66	77.44	74.62	74.52	75.85	77.97	75.83
Medium Difficulty	53.92	56.58	55.97	54.52	55.27	56.42	56.08	53.63
High Difficulty	44.27	46.95	46.65	44.57	44.79	47.50	46.48	44.05
Total	57.86	60.07	60.02	57.91	58.20	59.93	60.18	57.84

[1]Means are percentage correct.

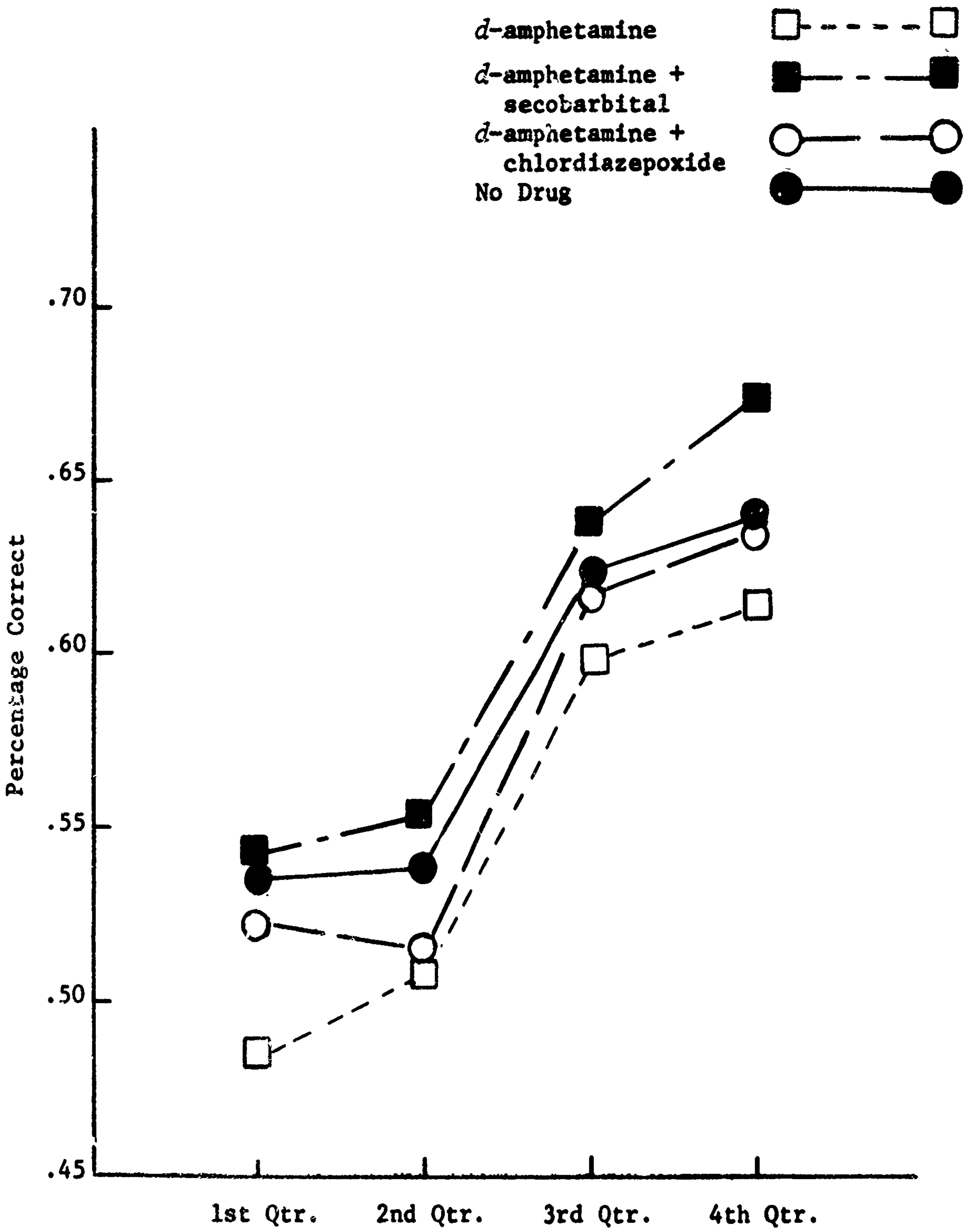

Fig. 4. PSMT Performance vs. Time After Drug Ingestion, Low Stress Condition (Experiment II)

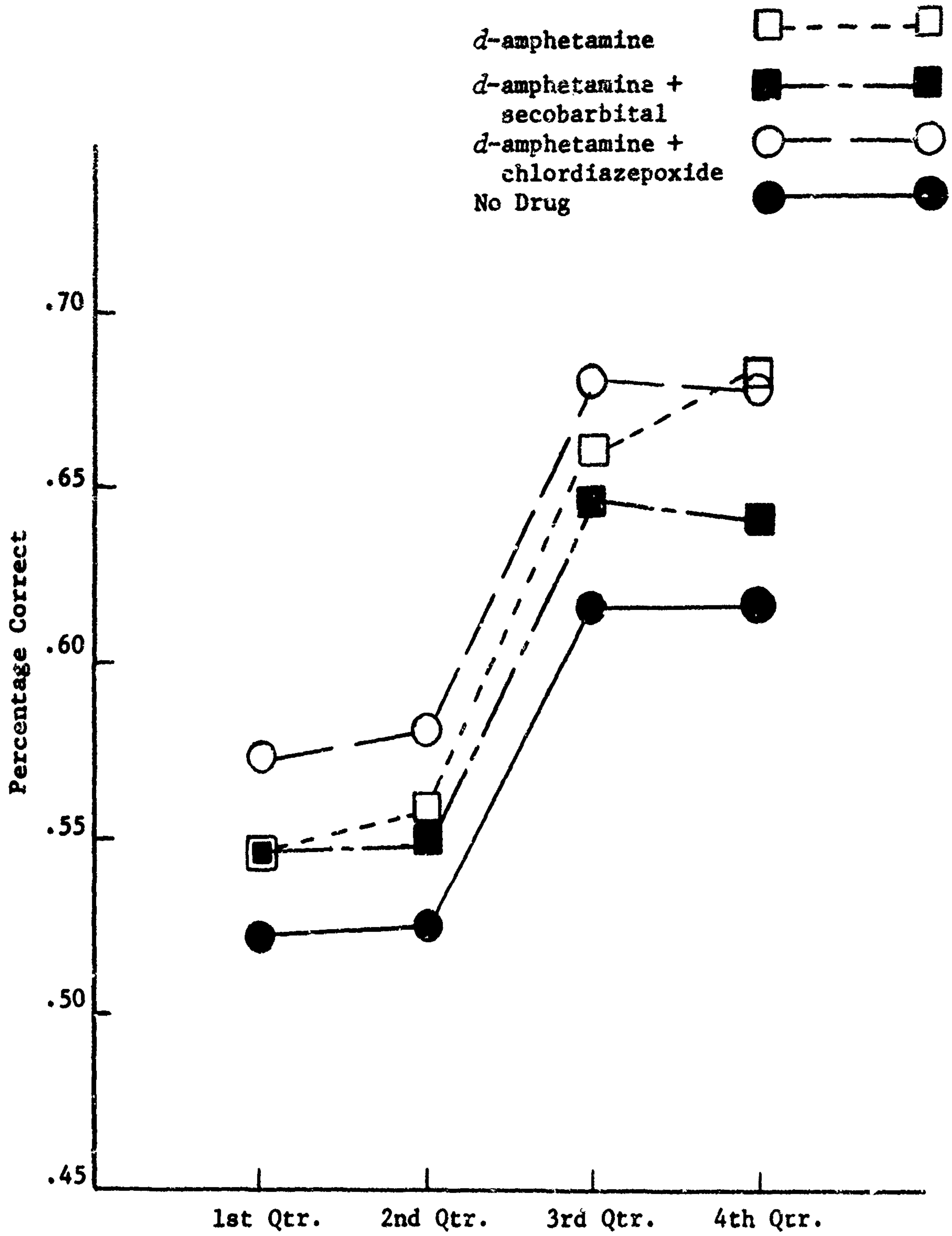

Fig. 5. PSMT Performance vs. Time After Drug Ingestion,

High Stress Condition

(Experiment II)

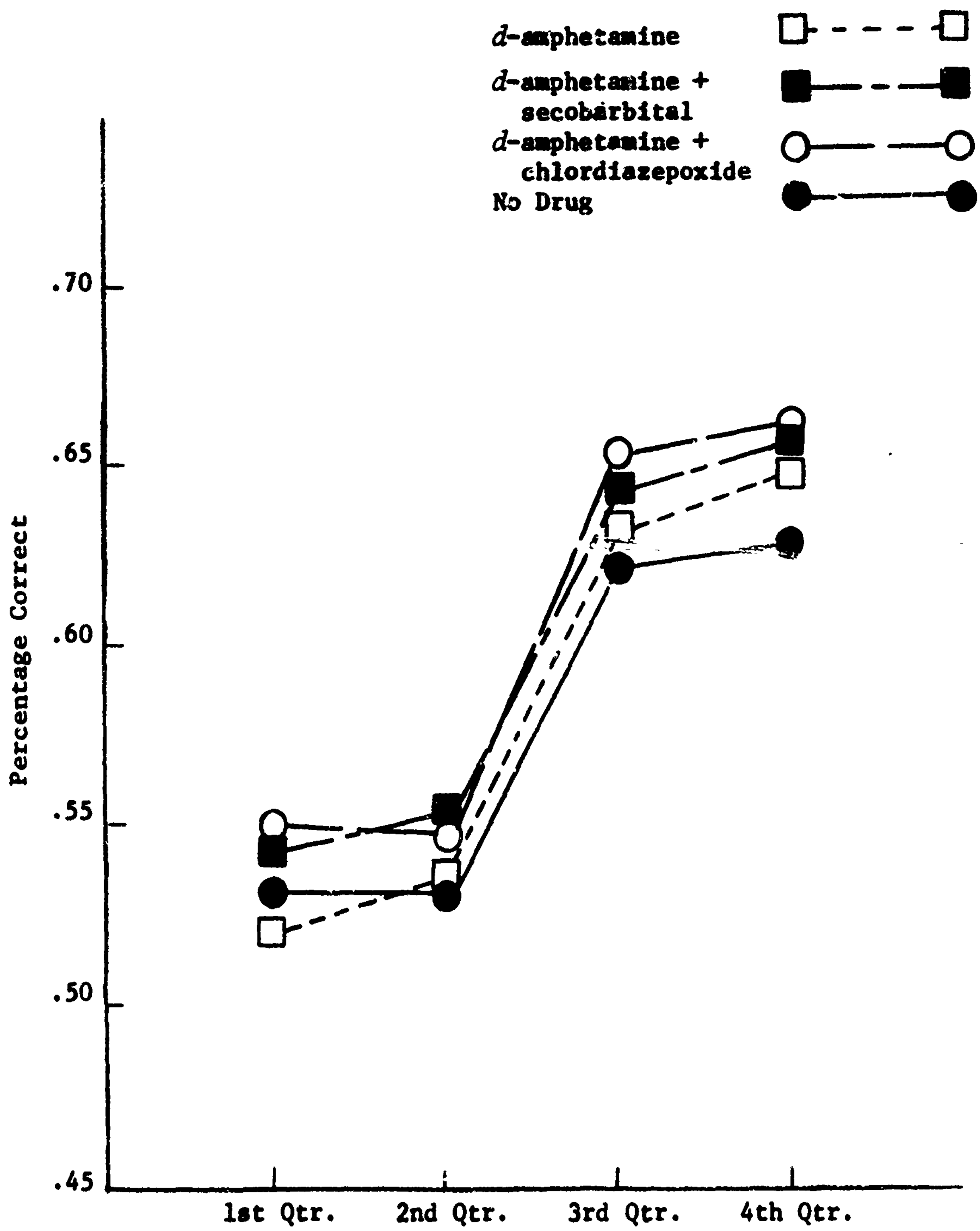

Fig. 6. PSMT Performance vs. Time After Drug Ingestion, Total Scores

(Experiment II)

Table 9

Judgment: Actual and Estimated PSMT Total Score (in Per Cent)

(Experiment II)

	d-amphetamine 10 mg.	*d*-amphetamine, 10 mg. plus Secobarbital, 50 mg.	*d*-amphetamine, 10 mg. plus Chlordiazepoxide, 10 mg.	No Drug
Actual	58.20	59.93	60.18	57.84
Estimated	-12.49	- 5.06	- 5.42	- 6.32
(N)	(16)	(16)	(15)	(16)

A positive overall placebo effect upon judgment was obtained, at $p<.05$. Subjects who had been given capsules before testing showed less of the downward bias (-4%) than those given capsules after testing (-10%). This placebo effect showed a significant interaction ($p<.05$) with drug conditions, being upward for D + S, D + C, and ND but downward for D.

Mood (MACL)

Significant treatment effects were obtained with 7 of the 11 mood factors in the first MACL, given 45 minutes after drug ingestion (immediately before the PSMT). No significant treatment effects were obtained in the second administration of the MACL (at t_1 + 140 minutes). Three factors yielded significant treatment effects in the third administration (at t_1 + 165 minutes). (See Table 10.)

Significant drug effects upon mood are summarized in Tables 11 and 12. Paired comparisons are reported only for factors showing significant overall F-ratios between drugs. The temporal courses of these mood effects are plotted in Figures 7 and 8.

The first MACL also yielded significant results for the incentive variable, with "variable payoff" groups exceeding "fixed payoff" groups in anxiety ($p<.01$) and concentration ($p<.005$), while being lower in "sociability" ($p<.005$). Positive placebo effects were obtained for surgency ($p<.05$), sociability ($p<.05$), egotism ($p<.01$), and elation ($p<.05$). A negative placebo effect was obtained for concentration ($p<.005$).

Table 10

Mood Main-Effects Means and Significant F-Ratios*

(Experiment II)

Table 10a. Mood #1

Factor	Fixed Payoff B_1	Variable Payoff B_2	"Drug Early" C_1	"Drug Late" C_2	*d*-amphetamine	*d*-amphetamine plus Secobarbital	*d*-amphetamine plus Chlordiazepoxide	No Drug	F-Ratio
Agg.	4.00	4.10	4.12	4.00	3.72	4.06	4.31	4.05	
Anx.	4.12	5.04	4.29	4.87	5.12	3.91	4.94	4.40	$B_2 >> B_1$
Sur.	7.98	7.37	8.19	7.16	7.19	8.12	8.12	7.35	$C_1 > C_2$
Conc.	7.53	8.78	7.53	8.78	7.53	8.09	8.53	8.40	$B_2 >>> B_1$ $C_2 >>> C_1$
Fat.	6.65	6.54	6.76	6.43	6.56	6.41	6.12	7.15	
Soc.	8.32	7.16	8.16	7.32	7.62	7.94	8.50	7.08	$B_1 >>> B_2$ $C_1 > C_2$
Sad.	4.15	3.90	3.82	4.22	4.12	3.91	3.78	4.22	
Ego.	4.99	5.06	5.47	4.57	4.44	4.72	5.66	5.22	$C_1 >> C_2$
Ela.	6.62	6.15	6.79	5.97	5.97	6.88	6.84	5.95	$C_1 > C_2$
Vig.	7.18	6.75	6.91	7.01	6.47	7.03	7.88	6.58	
Bold.	8.43	7.88	8.28	8.03	7.56	7.75	9.00	8.28	

$>$ = $p<.05$
$>>$ = $p<.01$
$>>>$ = $p<.005$

*Significant differences for incentive and placebo conditions are presented here. See Tables 11 and 12 for any drug paired comparisons.

Table 10b. Mood #2

Factor	Fixed Payoff B_1	Variable Payoff B_2	"Drug Early" C_1	"Drug Late" C_2	*d*-amphetamine	*d*-amphetamine plus Secobarbital	*d*-amphetamine plus Chlordiazepoxide	No Drug	F-Ratio
Agg.	3.99	4.26	4.09	4.16	3.59	4.19	4.25	4.40	
Anx.	3.96	4.31	4.00	4.26	4.03	3.81	4.53	4.15	
Sur.	6.32	5.84	6.31	5.85	5.75	6.69	6.00	5.92	
Conc.	7.15	7.09	7.09	7.15	7.00	7.25	7.06	7.15	
Fat.	7.47	6.85	6.90	7.43	6.31	6.75	7.38	8.00	
Soc.	7.01	6.25	6.79	6.47	6.62	7.12	6.3[illegible]	6.48	
Sad.	3.88	4.40	3.96	4.32	3.50	4.19	4.53	4.30	
Ego.	4.47	4.40	4.63	4.24	3.81	4.53	4.72	4.62	
Ela.	5.59	5.35	5.81	5.13	5.09	5.97	5.53	5.32	
Vig.	5.35	5.57	5.59	5.34	5.50	5.84	5.34	5.22	
Bold.	7.12	6.34	7.06	6.40	6.47	6.88	6.75	6.80	

Table 10c. Mood #3

Factor	Fixed Payoff B_1	Variable Payoff B_2	"Drug Early" C_1	"Drug Late" C_2	*d*-amphetamine	*d*-amphetamine plus Secobarbital	*d*-amphetamine plus Chlordiazepoxide	No Drug	F-Ratio
Agg.	3.84	3.36	3.65	3.54	3.25	3.75	3.59	3.75	
Anx.	3.93	3.46	3.56	3.82	3.65	3.44	4.06	3.62	$B_1 > B_2$
Sur.	7.06	6.68	7.41	6.32	6.97	6.88	6.66	6.95	$C_1 > C_2$
Conc.	6.04	6.13	6.01	6.16	5.86	6.34	5.97	6.15	
Fat.	6.56	5.97	6.21	6.32	5.91	6.44	6.53	6.20	
Soc.	7.07	7.01	7.35	6.74	7.09	7.31	6.59	7.15	
Sad.	3.65	3.44	3.35	3.74	3.12	3.41	4.16	3.50	
Ego.	4.44	4.53	4.79	4.18	4.00	4.47	4.53	4.85	
Ela.	5.69	5.53	5.97	5.25	5.31	5.94	5.47	5.70	
Vig.	5.84	5.69	5.97	5.56	5.44	5.69	5.56	6.25	
Bold.	6.88	6.40	6.81	6.47	6.38	6.88	6.19	7.02	

$>$ = $p<.05$

Table 11a

Mood ACL #1: Mean Total Scores for Boldness,

Differences[1] and "t" Values

(Experiment II)

	Mean	D	D+S	D+C	ND
d-amphetamine	7.56		0.36	2.74**	1.43
d-amphetamine plus Secobarbital	7.75	-0.19		2.39*	1.06
d-amphetamine plus Chlordiazepoxide	9.00	-1.44	-1.25		1.46
No Drug	8.28	-0.71	-0.52	0.72	

*p<.05

**p<.01

[1]Differences are column means minus row means.

Table 11b

Mood ACL #1: Mean Total Scores for Egotism, Differences[1] and "t" Values (Experiment II)

	Mean	D	D+S	D+C	ND
d-amphetamine	4.44		0.58	2.52*	1.72
d-amphetamine plus Secobarbital	4.72	-0.28		1.94	1.10
d-amphetamine plus Chlordiazepoxide	5.66	-1.22	-0.94		0.94
No Drug	5.22	-0.79	-0.51	0.43	

*p<.05

[1]Differences are column means minus row means.

Table 11c

Mood ACL #1: Mean Total Scores for Anxiety,
Differences[1] and "t" Values
(Experiment II)

	Mean	D	D+S	D+C	ND
d-amphetamine	5.12		2.51*	0.39	1.57
d-amphetamine plus Secobarbital	3.91	1.22		2.12*	1.07
d-amphetamine plus Chlordiazepoxide	4.94	0.19	-1.03		1.17
No Drug	4.40	0.72	-0.49	0.54	

*p<.05

[1]Differences are column means minus row means.

Table 11d

Mood ACL #1: Mean Total Scores for Sociability,

Differences[1] and "t" Values

(Experiment II)

	Mean	D	D+S	D+C	ND
d-amphetamine	7.62		0.57	1.60	1.06
d-amphetamine plus Secobarbital	7.94	-0.31		1.03	1.66
d-amphetamine plus Chlordiazepoxide	8.50	-0.88	-0.56		2.75**
No Drug	7.08	0.55	0.86	1.42	

**p<.01

[1]Differences are column means minus row means.

Table 12

Mood ACL #3: Mean Total Scores for Sadness

Differences[1] and "t" Values

(Experiment II)

	Mean	D	D+S	D+C	ND
d-amphetamine	3.12		0.87	3.20**	1.23
d-amphetamine plus Secobarbital	3.41	-0.28		2.32*	0.03
d-amphetamine plus Chlordiazepoxide	4.16	-1.03	-0.75		2.15*
No Drug	3.50	-0.38	-0.09	0.66	

*p<.05

**p<.01

[1]Differences are column means minus row means.

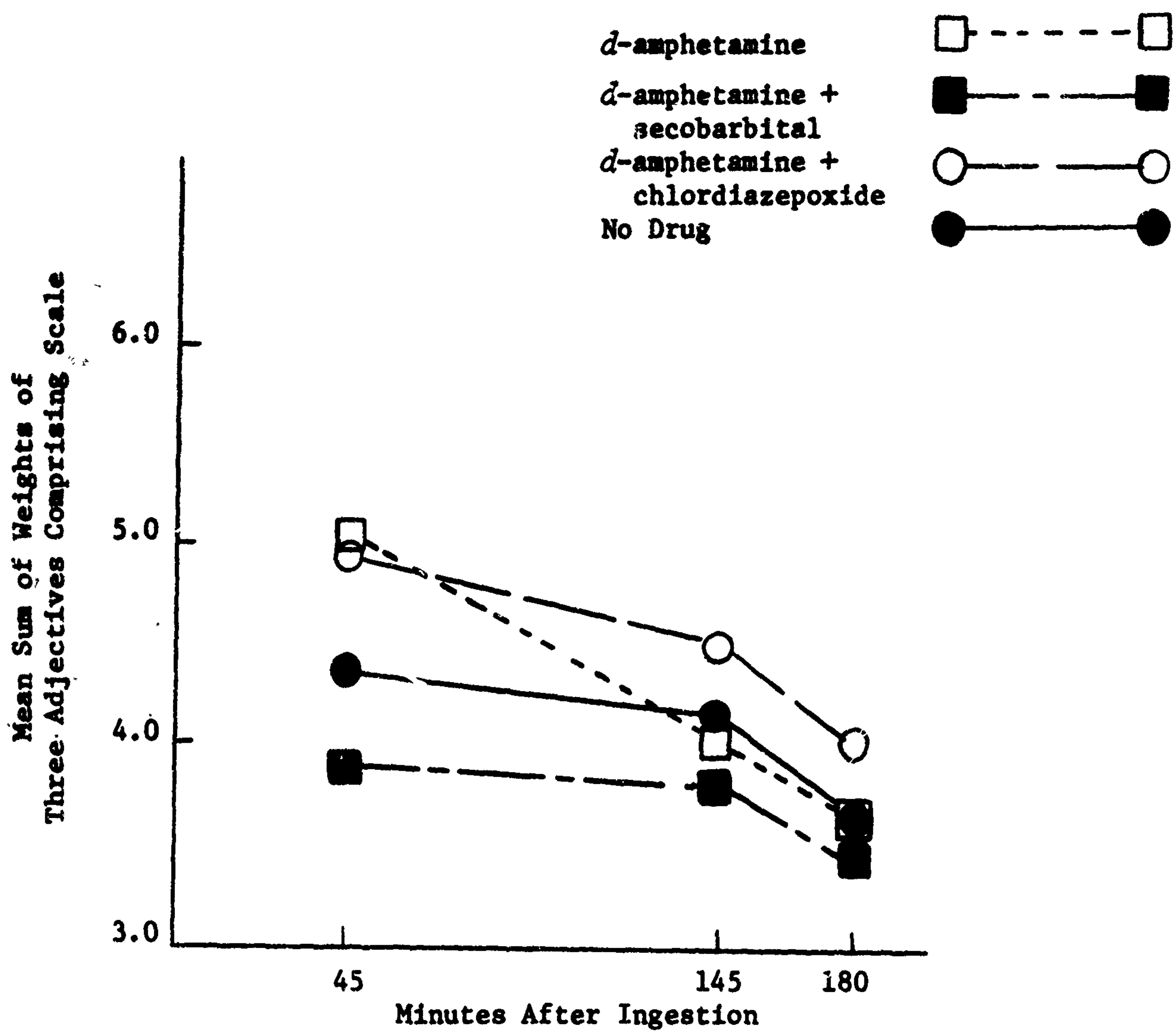

Fig. 7a. Mood ACL: Anxiety Scores vs. Time After Drug Ingestion

(Experiment II)

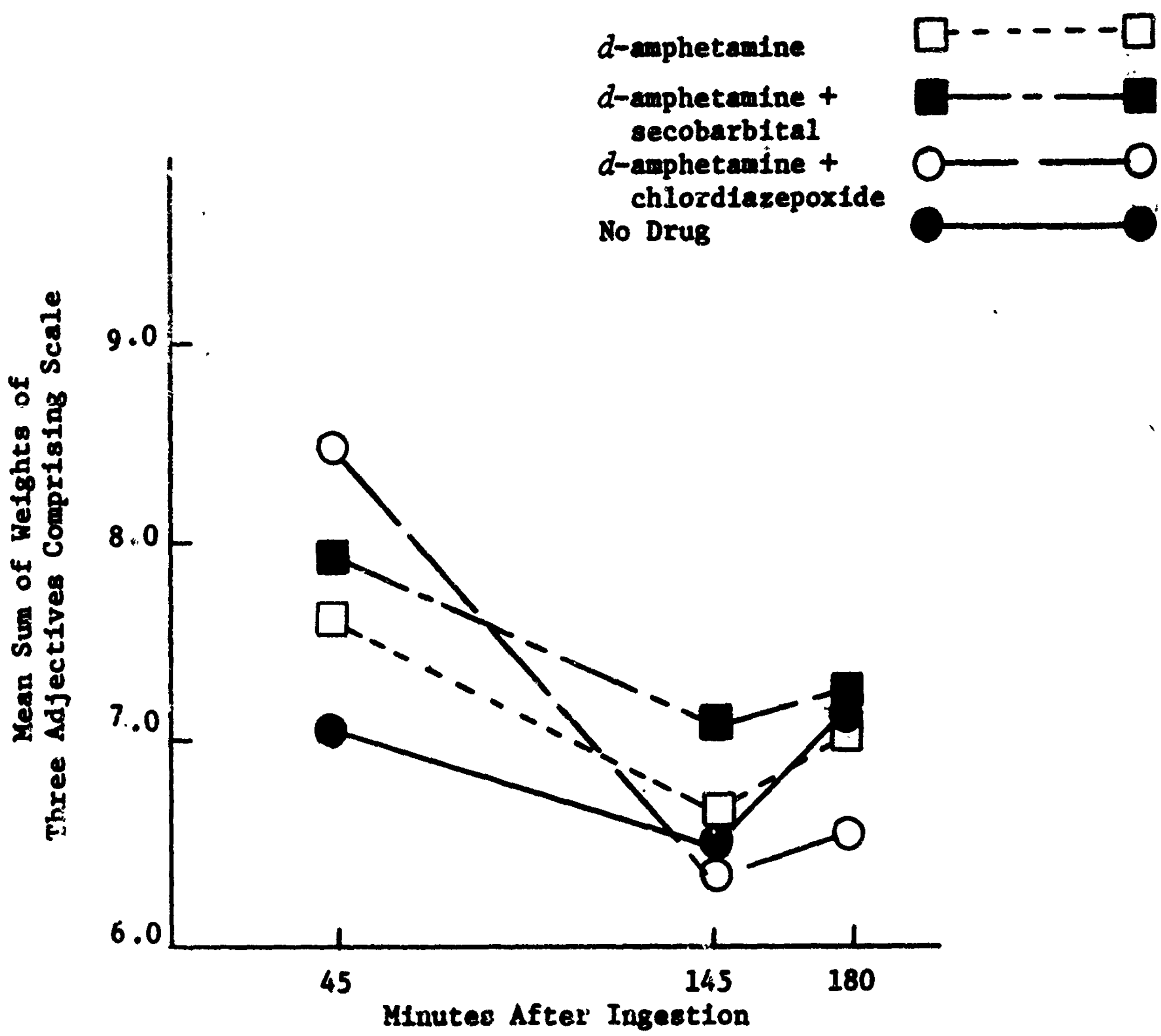

Fig. 7b. Mood ACL: Sociability Scores vs. Time After Drug Ingestion (Experiment II)

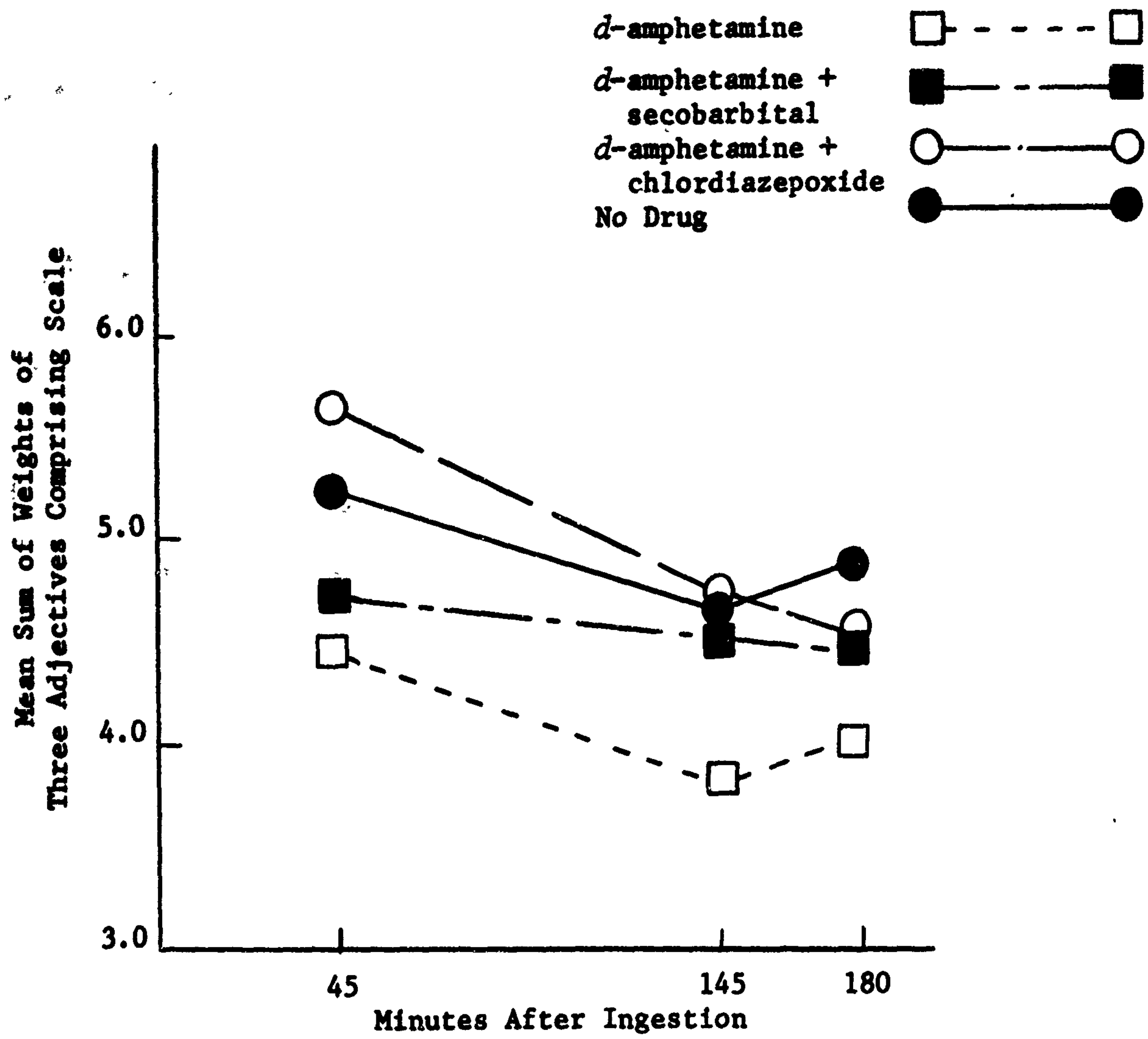

Fig. 7c. Mood ACL: Egotism Scores vs. Time After Drug Ingestion

(Experiment II)

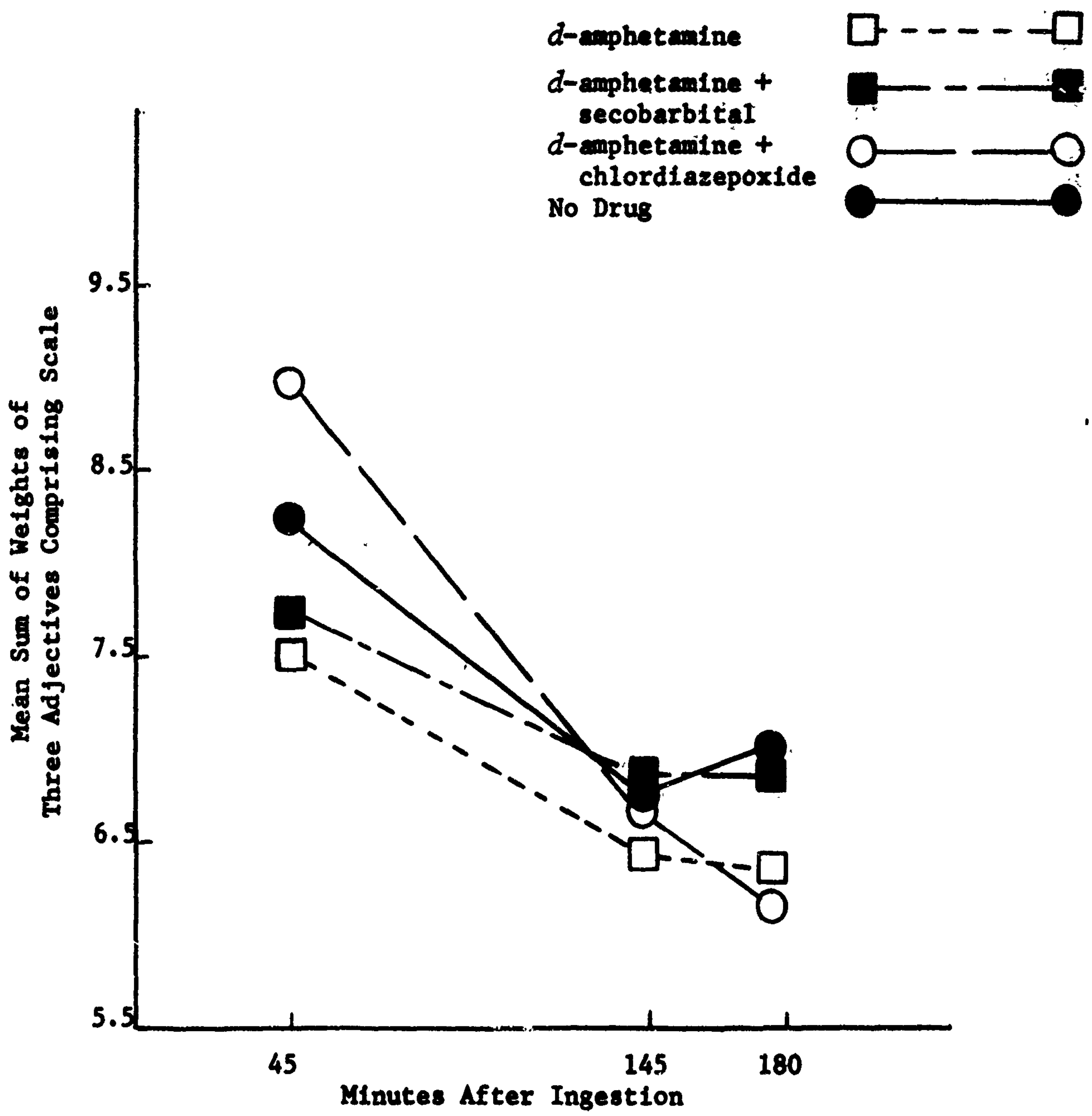

Fig. 7d. Mood ACL: Boldness Scores vs. Time After Drug Ingestion (Experiment II)

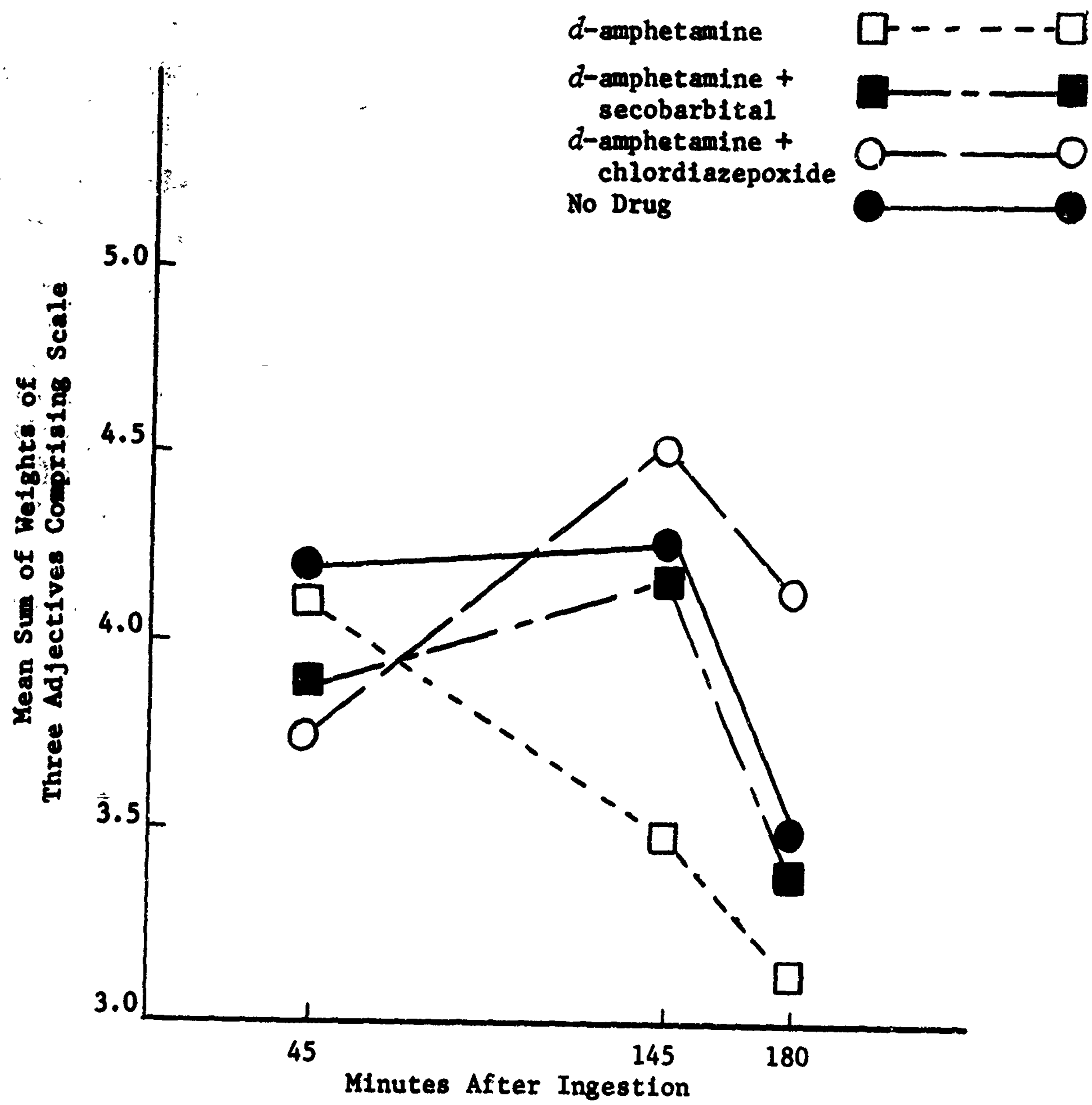

Fig. 8. Mood ACL: Sadness Scores vs. Time After Drug Ingestion (Experiment II)

The third MACL showed significant drug effects only for "sadness." (See Table 12.) The variable payoff groups were now less anxious ($p<.05$) than the fixed payoff groups. Since this MACL was given after the "drug late" groups had also been given their placebo capsules, no placebo effect as such can be measured, although "drug late" groups were lower in surgency ($p<.05$) than "drug early" groups.

On each of the three administrations of the MACL, a number of significant interactions were obtained for drugs x incentive, drugs x placebo effect, and/or incentive x placebo effect. A total of 10 such interactions were significant at $p<.05$ or beyond. On the basis of chance, we should have expected about 5 interactions to be significant, out of the 99 analyzed. With this reservation, the cell means of "significant" interactions are presented. (See Table 13.)

Time Perception Bias

No significant drug, incentive, or placebo effects were obtained in either administration of this test. The observed differences are at most midly suggestive of lengthening of apparent time duration by *d*-amphetamine. The selected D-ND comparison was not significant. (See Table 14.)

Taste Perception

Addition of either D + S or D + C to the coffee caused it to be rated significantly more bitter ($p<.01$) and less sweet ($p<.05$), as opposed to D or ND. Again, the mean differences were not overwhelming (about two units on the ten-point scale), and all ratings were we-l

Table 13

Mood ACL: Means of Significant Interactions ($p<.05$)

(Both Sessions) (Experiment II)

Table 13a

(First Administration)

Mood Factors	CE[1]	CL[2]
Surgency		
d-amphetamine, 10 mg.........	7.25	7.13
d-amphetamine, 10 mg. plus Secobarbital, 50 mg...	7.88	8.38
d-amphetamine, 10 mg. plus Chlordiazepoxide, 10 mg....	9.44	6.81
No Drug.....................	8.20	6.50
Sociability		
Fixed Payoff................	9.12	7.53
Variable Payoff.............	7.21	7.12
Concentration		
Fixed Payoff................	6.47	8.59
Variable Payoff.............	8.59	8.97

[1]CE = Capsule Early

[2]CL = Capsule Late

Table 13b

(Second Administration)

(Experiment II)

Mood Factors	CE[1]	CL[2]
Sadness		
Fixed Payoff.................	3.97	3.79
Variable Payoff.............	3.94	4.85
Sociability		
Fixed Payoff.................	7.53	6.50
Variable Payoff.............	6.06	6.44

[1]CE = Capsule Early

[2]CL = Capsule Late

Table 13c

(Third Administration)

(Experiment II)

Mood Factors	CE[1]	CL[2]
Aggression		
d-amphetamine, 10 mg. (D)....	3.44	3.06
d-amphetamine, 10 mg. plus Secobarbital, 50 mg. (D + S)............	4.25	3.25
d-amphetamine, 10 mg. plus Chlordiazepoxide, 10 mg. (D + C)............	3.19	4.00
No Drug (ND)................	3.70	3.80
Anxiety		
D...........................	4.00	3.31
D + S.......................	3.50	3.38
D + C.......................	3.44	4.69
ND..........................	3.35	3.90
Surgency		
D...........................	7.44	6.50
D + S.......................	6.38	7.38
D + C.......................	8.25	5.06
ND..........................	7.55	6.35
Elation		
D...........................	5.31	5.31
D + S.......................	5.75	6.13
D + C.......................	6.44	4.50
ND..........................	6.30	5.10
	FPO[3]	VPO[4]
Elation		
D..........................	5.69	4.94
D + S......................	6.06	5.81
D + C......................	4.69	6.25
ND.........................	6.20	5.20

[1]CE = Capsule Early

[2]CL = Capsule Late

[3]FPO = Fixed Payoff

[4]VPO = Variable Payoff

Table 14

Time Perception Bias[1]

(Experiment II)

Table 14a

Time Perception Bias, and Differences[2], First Testing

(t_i + 14' to t_i + 19')

	Mean	D+S	D+C	ND
d-amphetamine	3.66	0.62	0.15	0.62
d-amphetamine plus Secobarbital	4.28		-0.47	0.00
d-amphetamine plus Chlordiazepoxide	3.81			0.47
No Drug	4.28			

[1]Bias = number of overestimates minus number of underestimates.

[2]Differences are column means minus row means.

Table 14b

Time Perception Bias[1] and Differences[2], Second Testing

(t_i + 131' to t_i + 136')

(Experiment II)

	Mean	D+S	D+C	ND
d-amphetamine	4.41	-0.69	-0.63	-0.71
d-amphetamine plus Secobarbital	3.72		0.06	-0.02
d-amphetamine plus Chlordiazepoxide	3.78			-0.08
No Drug	3.70			

[1]Bias = number of overestimates minus number of underestimates.

[2]Differences are column means minus row means.

within the subjects' reported ranges of experience with coffee.

Discussion

Of the three hypotheses concerning the drugs' effects upon performance none was supported at a significant level. Although the drug main effect means and the drug x stress means were generally in the predicted orders, the failure of significance is at variance with the results of Experiment I, in which *d*-amphetamine yielded some significant improvements over no drug. This is rather surprising in view of the fact that a larger number of subjects was employed (136 vs. 63 in Experiment I). Lack of significance was probably not due to any antagonism of *d*-amphetamine by the additives in D + S and D + C, since the D + S and D + C conditions yielded means slightly exceeding D. The two important procedural changes (increasing payoff variance in "variable payoff" groups, and eliminating the pretest given under "no payoff") were expected to increase stress effects. Since stronger drug effects had previously been observed under the higher stress conditions, these changes were predicted to increase the opportunity for drug enhancement.

A further discrepancy was obtained regarding bias in judgment of performance, with no significant drug effect being obtained. Although based on a rather small sample of subjects, comparison of D with ND is surprising: the *d*-amphetamine mean was in the pessimistic direction. Reasons for this discrepancy with Smith and Beecher (1964) are not obvious.

Failure to obtain any significant differences in apparent time duration was also surprising, especially for D vs. ND, considering the

lengthening effects reported by Goldstone, Boardman and Lhamon (1958) and Frankenhauser (1958).

Drug effects upon mood, as measured by the Nowlis MACL, were more in accord with our expectations, although it was surprising that significance was largely limited to the first administration. That "anxiety" should be increased by D but reduced by D + S is not unexpected. Although D + C did not differ much from D or ND in "anxiety," it was the only drug condition to produce a reliable increase over ND with regard to "sociability," "egotism," or "boldness."

The most noteworthy feature of the MACL results is the striking difference in profiles between D + S and D + C. It would appear that chlordiazepoxide may, in some respects, show synergistic characteristics with *d*-amphetamine that are different from D + S. It is also noteworthy that both "boldness" and "anxiety" are significantly higher with D + C than with D + S. The significantly greater "sadness" for D + C (opposed to D or D + S), obtained in the third MACL, is enigmatic.

The reliabilities of the various mood effects can be further assessed by comparing results with those obtained in Experiment I, which utilized the same MACL except for the "boldness" index. Comparisons must be qualified by the fact that the MACL was administered at different times: $t_1 + 5'$, $t_1 + 85'$, $t_1 + 175'$ in Experiment I vs. $t_1 + 45'$, $t_1 + 140'$, and $t_1 + 165'$ in Experiment II. The placebo conditions were similar and the incentive conditions roughly similar. The only common drug comparison is D-ND.

In Experiment I, the first MACL ($t_1 + 5'$) predictably failed to yield any significant D-ND differences. The third MACL ($t_1 + 175'$) also failed to yield any significant drug effects. The second MACL

yielded a significant ($p<.01$) D-ND effect on vigor, and a highly significant ($p<.001$) negative ND-D effect on fatigue. There was also a fairly sizeable non-significant D-ND difference on anxiety.

None of the MACL administrations in Experiment II yielded significant D-ND effects upon vigor or fatigue. There was a moderate suggestion of a negative D-ND effect upon fatigue, but virtually no suggestion of a positive D-ND effect upon vigor. As noted, there was a significant D-ND effect upon anxiety. Thus, while no mood factor achieved significance in both experiments, there is moderate agreement that *d*-amphetamine increased anxiety and reduced fatigue. There is also agreement concerning the fact that virtually all drug-mood effects were dissipated to non-significance three hours after ingestion.

With regard to incentive and placebo effects, the only main effect common to both experiments was the significantly ($p<.001$ and $P<.01$) higher anxiety registered by the variable payoff groups on the MACL given immediately before the "payoff" test on the PSMT.

It would be tempting to speculate about causes of why the drug effects upon performance, judged performance bias, and apparent time duration did not conform to expectations. The most parsimonious interpretation, however, is in terms of sampling error.

In the PSMT the *d*-amphetamine mean total exceeded that of "no drug" by 7.96% ($p<.02$) in the data from the first test of Experiment I. In the second test its advantage was 4.89%. In Experiment II, the corresponding difference was 0.36%. It is possible that the true advantage of D over ND is about 3%-- enough to have produced statistical significance when lent a helping hand by sampling effects. Similar interpretations might well account for the deviations of our time and

performance judgment results from published data, although the significant placebo increase may give rise to some conjectures.

The effects of *d*-amphetamine, alone or with additives, would thus remain in doubt as far as the PSMT is concerned. Time and performance judgment effects are likewise questionable in this particular situation. About all that can be said with any confidence is that mood-relevant adjectives are differentially endorsed as a function of drug conditions, but even here it is not easy to conclude what is really going on (recalling that D + C produced reliable increases both in "boldness" and in "anxiety"). It may be that our results were generally depressed by defenses against being "under the influence" in this incentive-payoff situation. If so, such defenses do not seem to require the belief that a drug has been given.

The possibility of performance enhancement by *d*-amphetamine in task-induced "stress" situations seemed worthy of further exploration. Results thus far did not favor the expectation of very strong effects. It appeared unlikely that highly dramatic performance effects would be obtained in this laboratory "stress" situation either with performance, with judgment of performance, or with time estimation. However, the demonstration of any consistently reliable results would be of practical, as well as theoretical, importance. A more powerful experimental design therefore seemed called for.

Summary of Experiment II

This experiment was the second in a series designed to measure the joint effects of drugs and performance requirements upon task-induced stress. Dependent variables included performance at a paced

sequential memory task (PSMT), judgment biases concerning this performance, and mood ratings on the Nowlis MACL. The major hypotheses concern the relative roles of "psychoanaleptic" and "anti-stress" components in drug effects tested in this situation.

Experiment I had yielded some significant improvements of *d*-amphetamine over no-drug groups at the PSMT, with some indications that an anti-stress component was instrumental. Experiment II therefore included the previous dosage (10 mg.) of *d*-amphetamine, taken either alone, combined with 50 mg. sodium secobarbital, or combined with 10 mg. chlordiazepoxide HCl. The additives were predicted to yield increased stress-mitigation. These medications were compared with "no drug."

A total of 136 paid student volunteers were randomly assigned to the four drug groups. Half of each drug group received a placebo capsule before testing, and half did not. The active drugs were dissolved in decaffeinated coffee administered in the guise of a taste perception experiment to increase the procedure's plausibility. The medications were ingested 65 minutes before the start of the 50-minute test session with the PSMT.

Level of stress was manipulated by randomly assigning half of each drug x placebo group to a fixed payoff condition, and half to "incentive payoff" where the subjects' remuneration for the experiment was strongly dependent upon his performance in the PSMT. Thus, a factorial arrangement was achieved for drug x placebo x incentive conditions, similar to that employed in Experiment I.

No significant treatment effects were obtained with the PSMT.

Although all three drug treatments produced higher means than "no drug," the differences were smaller than previously obtained. Performance judgments were generally biased downward, although this bias was significantly ($p<.05$) reduced by the placebo effect. There was no significant drug or incentive effect upon this bias, although *d*-amphetamine showed a tendency to produce less favorable self-estimates of performance than any of the other drug/no-drug conditions, particularly when the placebo effect was also present. This finding is contrasted with that of Smith and Beecher (1964).

No significant treatment effects were obtained regarding bias in estimated time duration.

A number of significant treatment effects and interactions were observed with the various mood factors measured by the Nowlis MACL, with the drug combinations producing effects which were generally stronger, and sometimes opposite from, the effect of *d*-amphetamine taken alone. The *d*-amphetamine + chlordiazepoxide combination yielded a mood profile that differed strikingly from that of the *d*-amphetamine + secobarbital combination.

Experiment III

The goals of this study were as follows:

(1) To confirm or deny, with a more powerful experimental design, the previous trends suggesting that *d*-amphetamine enhances non-fatigued performance in the PSMT.

(2) To explore dosage variations in this drug: 10 mg. (D_{10}) and 15 mg. (D_{15}).

(3) To determine the interaction of drug effects with pacing

variations in the PSMT. (Storage load had previously been manipulated, but input pacing had not.)

(4) To compare, for the various medications, the PSMT results with those on a supplementary non-paced task that imposes no short-term storage requirements.

(5) To determine the sensitivities of both task to 100 mg. secobartibal (S_{100}), a "depressant" with potential anti-stress properties.

Hypotheses

H1: D_{15} will excel D_{10}, P or ND.

H2: D_{10} will excel P or ND.

H3: The overall gain produced by D_{15} or D_{10} over P or ND will not be accounted for on the basis of gains produced in the later parts of each test session, as would be expected from anti-fatigue effects.

H4: The gain produced by D_{15} or D_{10} over P or ND will grow smaller as the sequence of weekly sessions continues, as expected from adaptation to stress arousal.

Inclusion of secobarbital as a treatment condition was intended to explore treatment dynamics as related to response variations. Since the 100 mg. dosage was expected to act as a direct cognitive depressant as well as an anti-stress agent, no predictions of net performance effects could be made.

Dependent Variables

Pacing of PSMT imputs (2-second intervals vs. 3-second intervals) was counterbalanced throughout each 42-minute administration of this task, in order to permit independent within-subject assessments of rate

effects and serial effects. All sequences had a constant $\overline{SL}$ of 4.8, the highest of the three levels previously employed.

PSMT pacing variations were an exploratory measure. *D*-amphetamine, in its psychoanaleptic role, may exert some facilitative effect upon data-processing ability that is independent of the mitigation of emotional stress effects. Quantitative differentiation of cognitive and emotional roles requires location of a "dropoff" zone ascribable to emotional factors. Such a zone is defined as an interval bounded by points of inflection in the information input/output curve for a particular task. When such points are located with some confidence, it will be possible to generate predictions concerning relative effects of psychoanaleptic and anti-stress components as moderated by pacing variations. It was hoped that the higher input rate might enter this "dropoff" zone.

A second performance measure was a one-hour arithmetic task, involving the addition and subtraction of columns of signed numbers after the procedure of Holliday (1964). Although the time limit was known to the subjects, they were not paced, as in Holliday's procedure, they were required to record results from each separate step. This task was included to introduce new parametric variations (as, absence of pacing and storage requirements), and to determine whether the enhancement effects reported by Holliday (ibid.) could be obtained with non-sleep deprived subjects. Weiss and Laties (1962) cite two positive and two negative findings on arithmetic tasks with amphetamines, and conclude (p. 19) that "there is some evidence that caffeine and amphetamine can improve performance on arithmetic tasks, especially if the experimental sessions are long."

Separate scores were computed for accuracy and for number of problems completed correctly, although the subjects were aware that performance bonuses would depend only upon the latter of these indices.

In addition to these performance measures, time judgments were obtained as in Experiment II. Performance self-judgments (per cent correct) were obtained for each session in both the PSMT and arithmetic task to test for drug-induced bias. The MACL was augmented by an additional index of "boldness," devised by the authors.

Subjects

The subjects were recruited in the same manner as in Experiment I and II. None had participated in either of these earlier experiments. Before enrolling for the experiment, each subject was asked to examine a list of thirteen drugs from which his medications were to be selected, similar to that employed in Experiment II. The forty-eight subjects who completed the five sessions consisted of 40 males and 8 females. Median ages were 21.6 and 22.0, respectively.

Experimental Design

Since dramatic performance effects seemed unlikely, a sensitive design was indicated. A test-retest technique was selected. In a series of replications of two basic 5 x 5 Latin squares, each subject received each drug treatment once. Order of treatment was balanced within each square. The two squares, jointly, were also balanced for residual or "carryover" effects of the various drug treatments, although the test sessions were separated by one-week intervals. The scheme described by Williams (1949) was followed, except that each treatment

sequence was replicated with four to six different subjects.

This replication of the same two basic Latin squares was preferred to the use of a different square for each five subjects because dropouts were anticipated (and occurred) throughout the five-week course of the experiment. Incorporation of residual effects into the Latin square model complicates the usual processes of adjusting for missing data. Replication of the same squares permits use of the method of unweighted means by treating the group assigned to each sequence as if it were a single subject. This results in a very conservative estimate of error degrees of freedom, but yields an error mean square comparable to that produced by separate squares. The design of Experiment III is shown in Table 15.

The variable payoff ("high stress") condition was employed throughout. Since retesting was involved, drug disguisal was not attempted. The drug conditions were as follows:

1. *D*-amphetamine sulfate, 10 mg. capsule (D_{10})
2. *D*-amphetamine sulfate, 15 mg. capsule (D_{15})
3. Sodium secobarbital, 100 mg. capsule (S)
4. Placebo capsule (P)
5. No drug of placebo (ND)

Procedure

For the five four-hour sessions involved, each subject was shown the following schedule of payments:

For each session completed, the "base pay" was $3.00. For completion of all five sessions, a bonus of $15.00 would be awarded.

Table 15

Latin Square Design

(Experiment III)

No. Session	Ten Drug Sequences 1	2	3	4	5	6	7	8	9	10
1	ND	S	D10	D15	P	ND	S	D10	D15	P
2	S	D10	D15	P	ND	D10	D15	P	ND	S
3	D15	P	ND	S	D10	S	D10	D15	P	ND
4	P	ND	S	D10	D15	P	ND	S	D10	D15
5	D10	D15	P	ND	S	D15	P	ND	S	D10
No. of Subjects in Sequence	6	4	6	4	5	4	5	5	5	4

An additional bonus of $4.00 per session would be paid to the top 1/3 performers in each treatment group, and $2.00 per session to the middle 1/3. The performance bonuses would also be contingent upon completing all five sessions. A subject's performance score would represent the sum of his numbers of correct answers in the PSMT and the arithmetic task. He would receive his total payment after the entire experiment was finished, at which time he would be given a list of his scores with the corresponding bonus cutoff points, but not told what drugs he had actually received. Until then, no knowledge of results would be given.

The experiment took place on five successive Wednesday evenings. During each session, the timetable depicted in Table 16 was observed. Although the time of commencement of each session varied by as much as 15 minutes, the intervals following ingestion never varied by more than 2 minutes.

Subjects were assigned to the ten different treatment sequences according to numbered cards dealt from a shuffled deck.

The "subjects blind" requirement was met by (1) using matched capsules and (2) telling subjects that they might receive the same drug twice (so that they would not expect a *necessarily* different effect on each successive test session). Scoring and checking of test results, although "objective," was carried out under blind conditions.

The remainder of the procedure generally paralleled that of Experiment II, except for the deletion of the "taste perception" test and the addition of the arithmetic test. (Compare Tables 7 and 16.) Self-judgments of per cent correct responses were elicited following

Table 16

Activity Schedule

(Experiment III)

Activity	Time (in minutes)
Drug Ingestion	$*t_i$
First Mood ACL	$t_i + 8$
First Time Perception Task	$t_i + 15$
Second Mood ACL**	$t_i + 50$
Memory Task	$t_i + 70$
Third Mood ACL	$t_i + 115$
Second Time Perception Task	$t_i + 120$
Arithmetic Task	$t_i + 143$
Dismissal	$t_i + 210$

$*t_i$ = time of ingestion

**Administered in Sessions 2-5 only.

the arithmetic task, as well as after the PSMT. One further provision was for the subject to indicate in writing, at the end of each evening session, whether the drug he had received this day affected him as a "stimulant," a "depressant," a "tranquilizer," or whether he perceived no drug effects. These categories were briefly explained, utilizing the energizer-psychoanaleptic concept for "stimulant," the sedative-hypnotic concept for "depressant," and the notion of a "tranquilizer" as something that "relieves tensions and anxieties without making you drowsy or impairing mental functions." Although the provision was made for reporting "no effect," the subjects were never told that they might get a placebo. General written comments were again solicited, at the end of the last day of testing, but this time with the option of anonymity.

Results

PSMT Performance

The overall "drug treatments" effect upon PSMT total correct was significant at $p<.001$. See Table 17 for analyses of variance. Paired comparisons with t-test outcomes are presented in Table 18.

It will be noted, in Table 17 and in the other analyses of variance for this experiment, that the sums of squares are partitioned in two alternative manners. Because of the entanglement of direct and residual effects, it is necessary either to add unadjusted direct effects to adjusted residual effects, or to do the converse operation. Since the adjusted value is, in each case, the appropriate one for testing, it is necessary to compute the results for each of the

Table 17

Analysis of Variance, PSMT Total Scores

(Experiment III)

Source of Variance	DF	SS	MS	F
Within Groups	5	3367.90	673.58	8.78****
Between Groups	4	3395.90	848.98	11.07****
Periods	4	22832.50	5708.12	74.41****
Treatments, Residuals not in Model	4	2429.60	607.40	
Residuals, Treatments not in Residuals	4	267.05	66.76	0.87
Treatments, Residuals not in Treatments	4	2512.61	628.15	8.19****
Residuals, Treatments not in Model	4	184.26	46.06	
Error, Residuals in Model	28	2147.95	76.71	
Error, Residuals not in Model	32	2415.00	75.47	
Totals	49	36855.90		

*$p<.05$
**$p<.02$
***$p<.01$
****$p<.001$

Table 18

Mean PSMT Total Scores (Percentage Correct), Differences[1] and "t" Values (Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	48.77%		2.50**	1.11	3.03***	0.25
Secobarbital	46.44%	2.33		3.61***	5.53****	2.25*
d-amphetamine, 10 mg.	49.80%	-1.03	-3.36		1.92	1.36
d-amphetamine, 15 mg.	51.59%	-2.82	-5.15	-1.79		3.28***
Placebo	48.53%	0.24	-2.09	1.27	3.06	

*p .05 - two-tailed test
**p .02
***p .01
****p .001

[1]Differences are column means minus row means.

alternative partitionings.

It can be seen that D_{15} produced a highly significant ($p<.01$) improvement of about 6% magnitude over P or ND. D_{10} was superior to P or ND, but not significantly so. It was inferior to D_{15} at $p<.10$ (two-tailed). S was significantly inferior to all other drug conditions, including P and ND. The superiority of D_{15} could not be accounted for strictly in terms of numbers of answers attempted (i.e., by increased willingness to guess). Subjects receiving D_{10} or D_{15} not only had more correct recalls, but also had slightly higher ratios of correct to incorrect recalls than they had with any of the other treatments. The corresponding ratios with S were slightly lower than with P or ND.

Separate analyses of variance for high-speed sequences and low speed sequences are presented in Tables 19 and 20, respectively. Paired comparisons with t-test results are presented, for high speed and low speed respectively, in Tables 21 and 22. Drug profiles for high speed and low speed sequences are compared in Figures 9 and 10. Drug means (total correct) for the five periods (successive weekly test sessions) are plotted in Figure 11. Within-period performance curves are given in Figure 12. Dosage-response curves are plotted in Figure 13.

The between periods effect was highly significant ($p<.001$) and yielded a composite "periods" curve (Figure 11) which has the properties of monotonic increase and negatively accelerated rate of increase.

Residual or carry-over effects from particular treatments to immediately succeeding sessions did not approach significance, suggesting that the one-week interval between test sessions was adequate to re-

Table 19

Analysis of Variance for PSMT High Speed Scores

(Experiment III)

Source of Variance	DF	SS	MS	F
Within Groups	5	799.99	160.00	8.67****
Between Groups	4	848.79	212.20	11.50****
Periods	4	6125.81	1531.45	82.96****
Treatments, Residuals not in Model	4	573.26	143.32	
Residuals, Treatments not in Residuals	4	98.54	24.63	1.33
Treatments, Residuals not in Treatments	4	625.13	156.28	8.47****
Residuals, Treatments not in Model	4	46.68	11.67	
Error, Residuals in Model	28	516.97	18.46	
Error, Residuals not in Model	32	615.51	19.24	
Totals	49	9578.87		

*p<.05
**p<.02
***p<.01
****p<.001

Table 20

Analysis of Variance, PSMT Low Speed Scores

(Experiment III)

Source of Variance	DF	SS	MS	F
Within Groups	5	1049.35	209.87	7.91****
Between Groups	4	976.15	244.04	9.20****
Periods	4	5334.56	1333.64	50.27****
Treatments, Residuals not in Model	4	657.20	164.30	
Residuals, Treatments not in Residuals	4	62.86	15.72	0.59
Treatments, Residuals not in Treatments	4	650.96	162.74	6.13***
Residuals, Treatments not in Model	4	69.10	17.28	
Error, Residuals in Model	28	742.82	26.53	
Error, Residuals not in Model	32	805.68	25.18	
Totals	49	16313.96		

*p<.05
**p<.02
***p<.01
****p<.001

Table 21

Mean PSMT High Speed Totals (Percentage Correct),

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	42.49%		2.39*	1.53	3.21***	0.39
Secobarbital	40.31%	2.18		3.92****	5.60****	2.78***
d-amphetamine, 10 mg.	43.88%	-1.39	-3.57		1.68	1.14
l-amphetamine, 15 mg.	45.41%	-2.92	-5.10	-1.53		2.82***
Placebo	42.84%	-0.35	-2.53	1.04	2.57	

*p<.05 - two-tailed test
**p<.02
***p<.01
****p<.001

[1]Differences are column means minus row means.

Table 22

Mean PSMT Low Speed Totals (Percentage Correct),
Differences[1] and "t" Values
(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	55.05%		2.26*	0.62	2.49**	0.76
Secobarbital	52.56%	2.49		2.88***	4.75****	1.51
d-amphetamine, 10 mg.	55.72%	-0.67	-3.16		1.87	1.37
d-amphetamine, 15 mg.	57.77%	-2.72	-5.21	-2.05		3.24***
Placebo	54 22%	0.83	-1.66	1.50	3.55	

*p .05 - two-tailed test
**p .02
***p .01
****p .001

[1]Differences are column means minus row means.

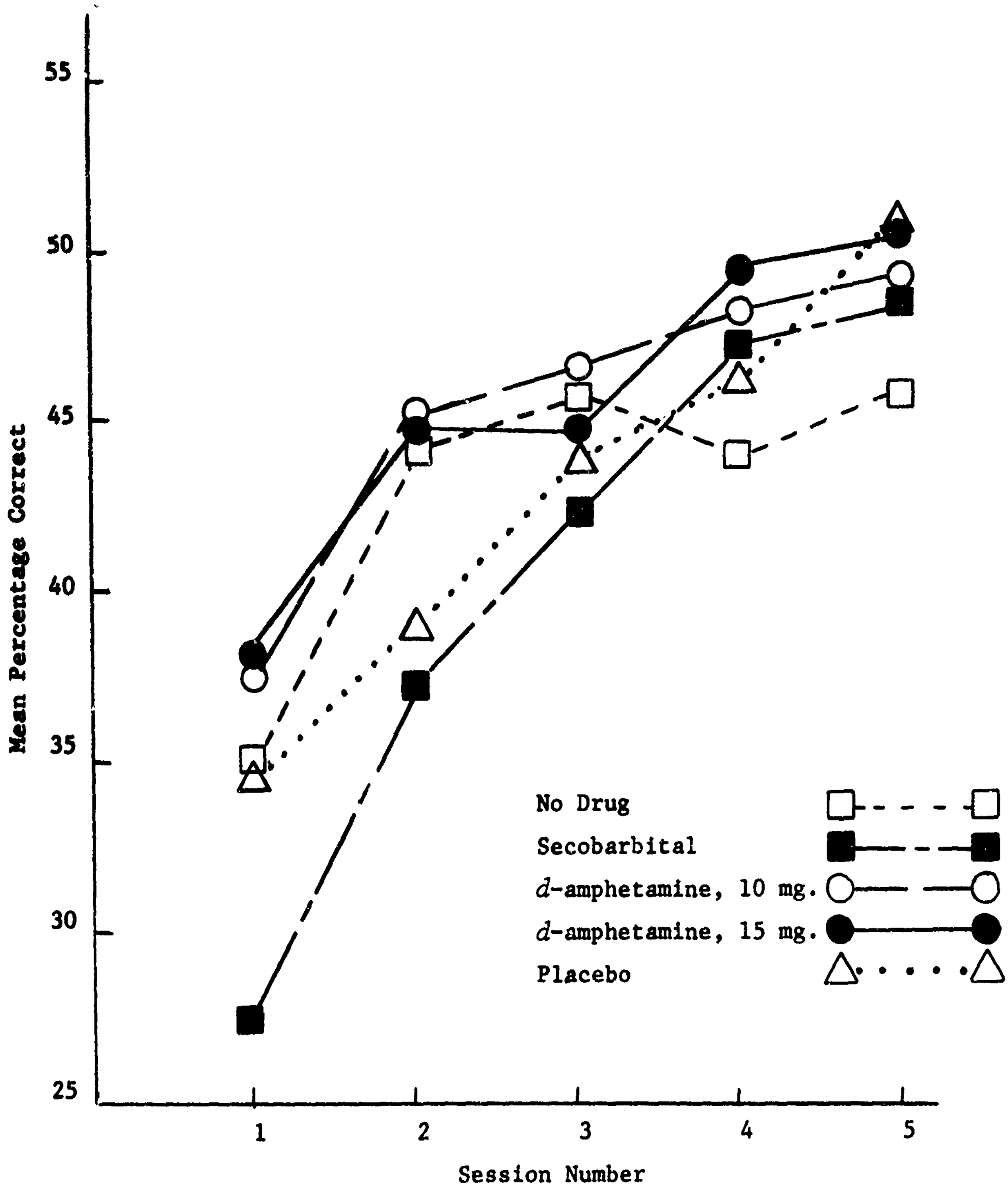

Fig. 9. High Speed Totals (PSMT) (Experiment III)

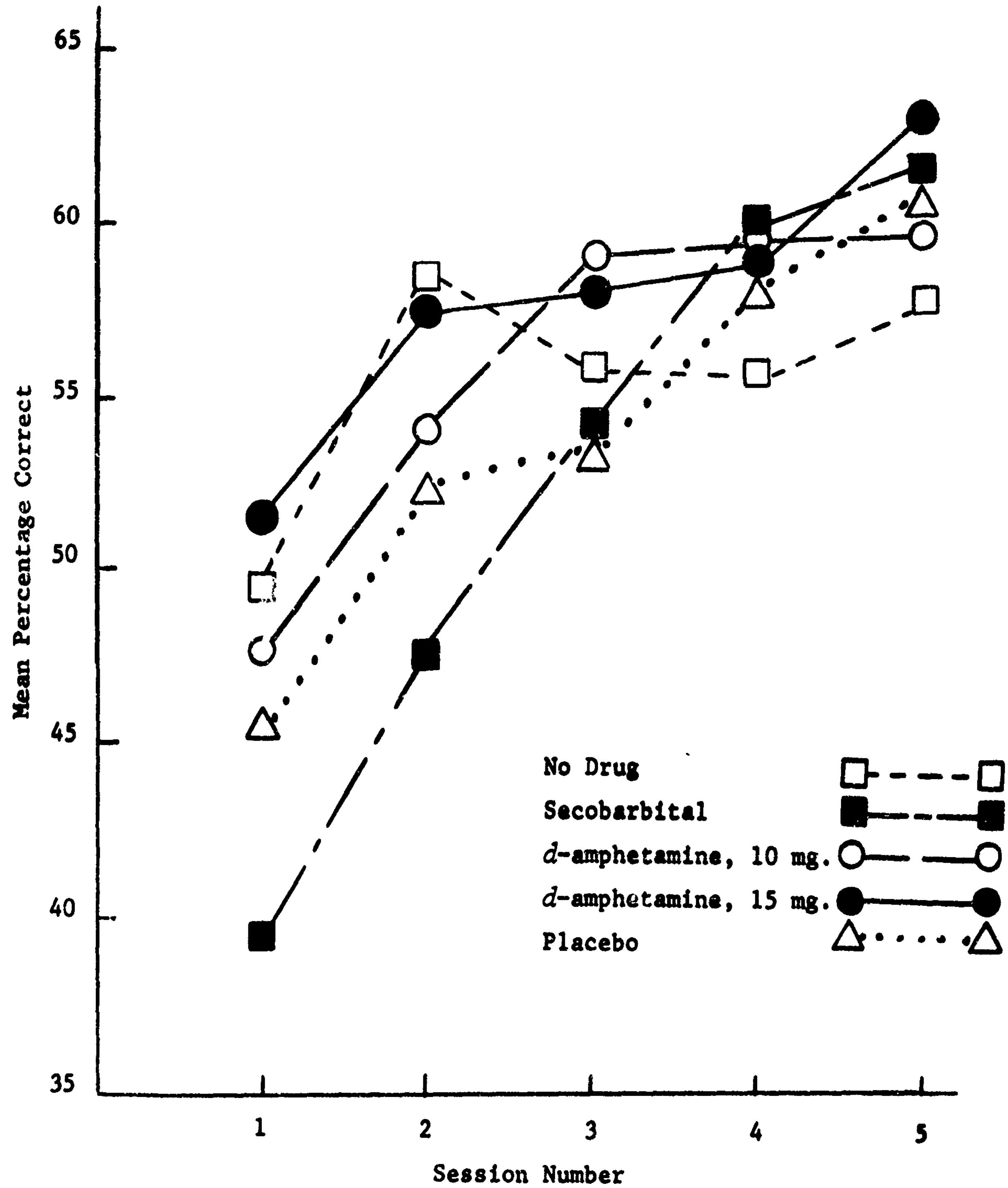

Fig. 10. Low Speed Totals (PSMT) (Experiment III)

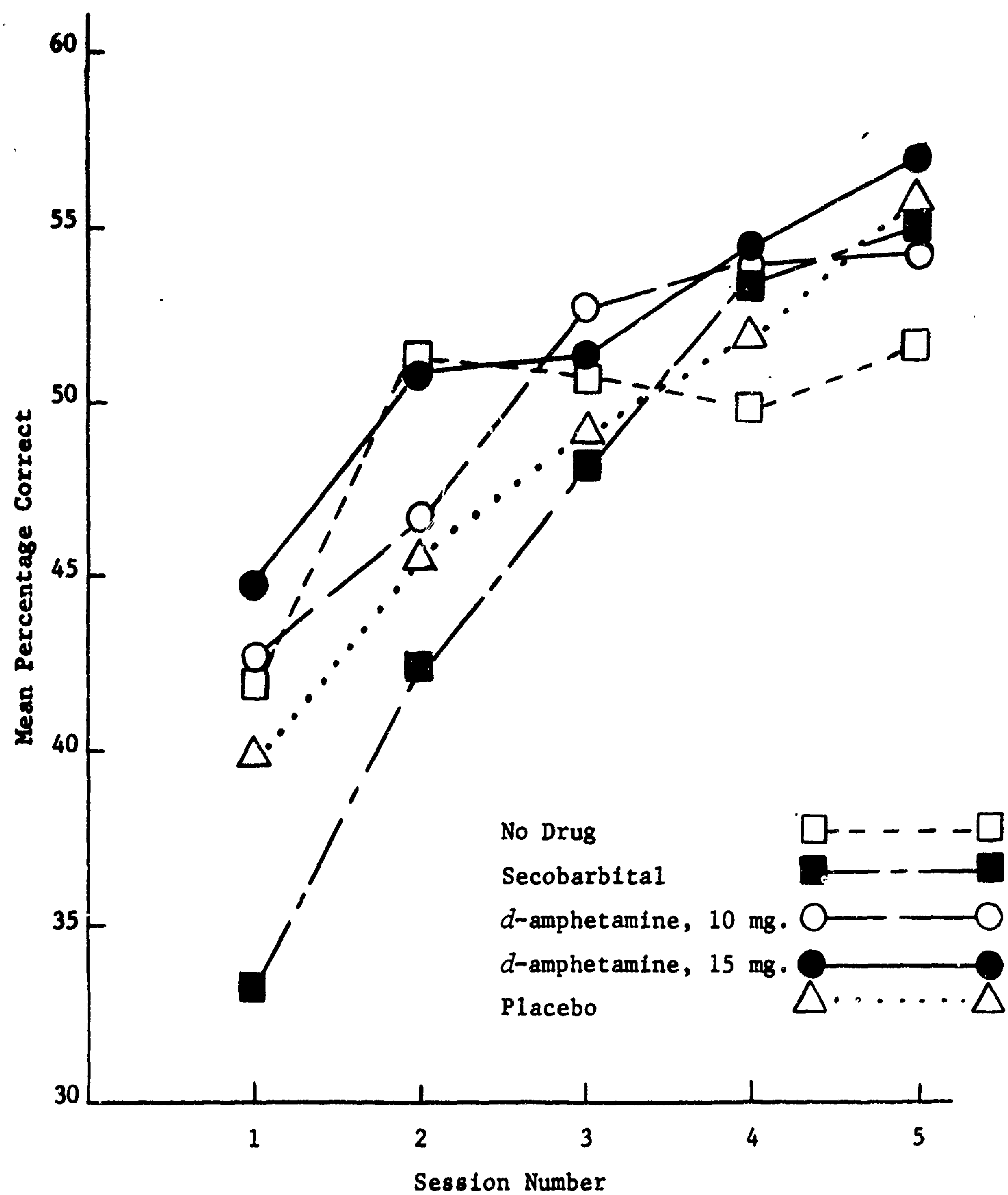

Fig. 11. Grand Totals (PSMT) (Experiment III)

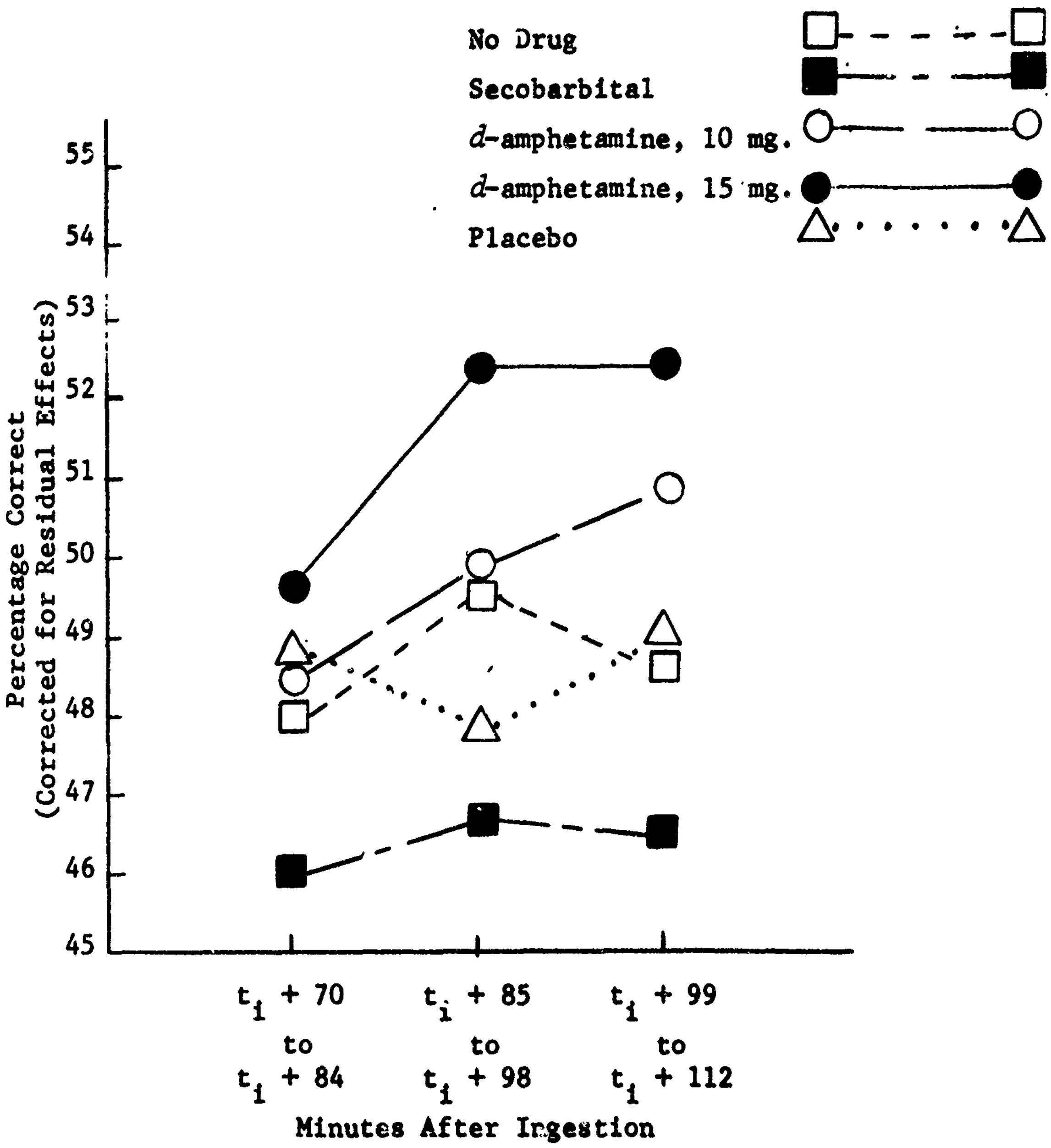

Fig. 12. Drug Curves by 1/3-Period Intervals, PSMT Total Scores (Scores pooled over test sessions). (Experiment III)

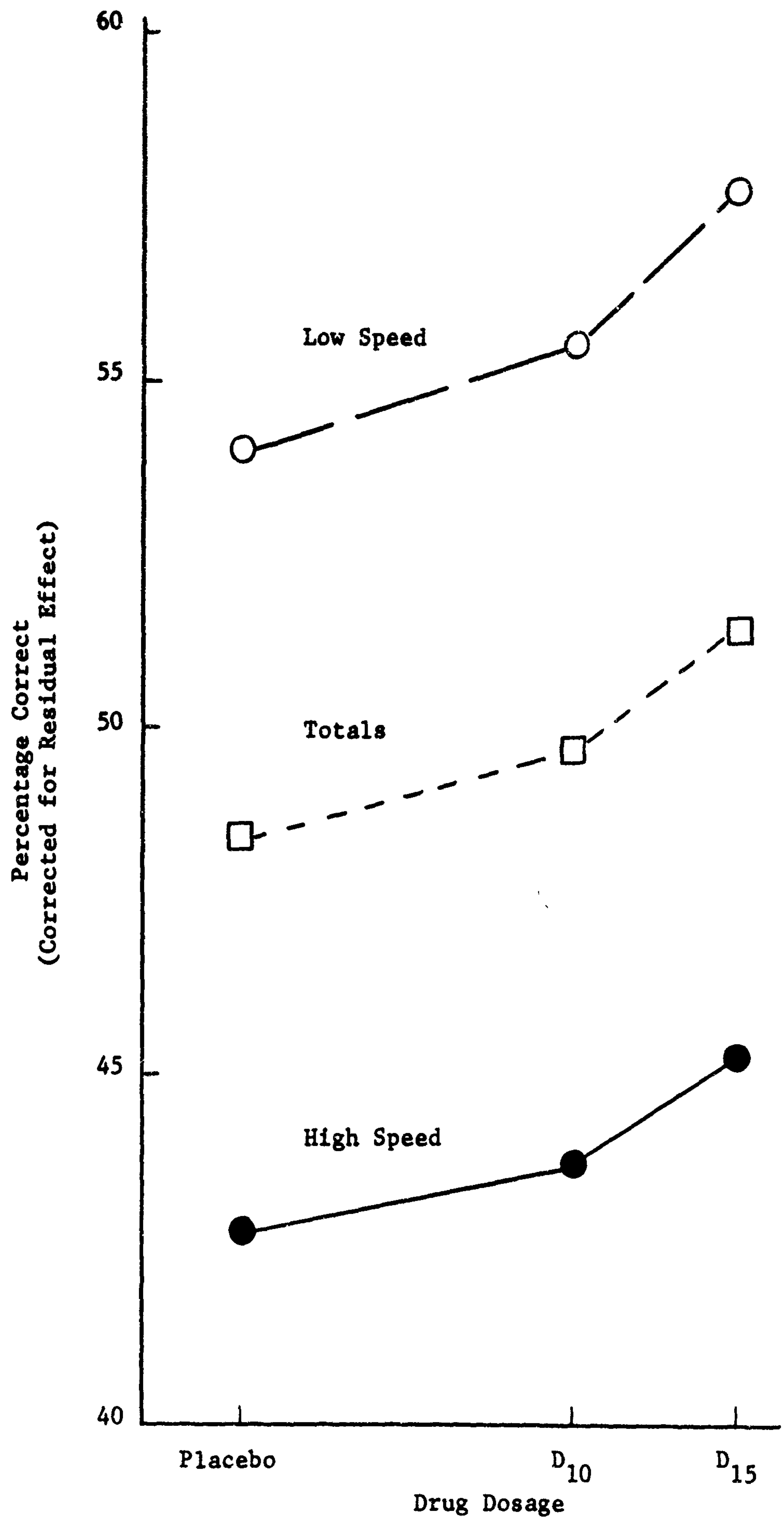

Fig. 13. Dose Response Curve--*d*-amphetamine with Placebo--PSMT Total Scores. (Experiment III)

move most of the effects of preceding drug treatments. (Refer to Table 17.) The directions of the residual effects is such as to yield a non-significant positive correlation with main effects ($r=.66$).

Comparison of PSMT results by input rates shows a mean displacement of about 12% in total correct responses between the low speed and the high speed sequences (3-second intervals vs. 2-second intervals). However, the drug treatment effects were independent of input rate, reaching comparable levels of significance with both rates. (Compare Tables 21 and 22.) This comparability was present during all 5 sessions. Note the similarity of drug curves over sessions between Figure 9 (high speed) and Figure 10 (low speed).

Within-session breakdowns by 14-minute intervals reveal a sharper initial slope for D_{15}, but it is not maintained. (See Figure 12.)

Arithmetic performance

As indicated in Tables 23 and 24, the drug effect F-ratio for arithmetic total correct was significant at $p<.001$, and the effect upon accuracy significant at $p<.01$. Paired comparisons with t-test results are presented in Tables 25 and 26 respectively. The respective drug profiles for total correct and accuracy for the 5 weekly test sessions are presented in Figures 14 and 15. Dosage-response curves are plotted in Figures 16 and 17.

In general, the drug effects upon total correct in the arithmetic task paralleled those observed with the PSMT. With this task, however, D_{10} as well as D_{15} yielded significant enhancement effects. A further difference, the failure of S to impair performance significantly, must be viewed in light of the greater time elapse after drug in-

Table 23

Analysis of Variance, Arithmetic Total Correct

(Experiment III)

Source of Variance	DF	SS		MS	F
Within Groups	5		551.20	110.24	1.61
Between Groups	4		3742.90	935.72	13.70****
Periods	4		39996.60	9999.15	146.38****
Treatments, Residuals not in Model	4	1867.60		466.90	
Residuals, Treatments not in Residuals	4	404.82		101.21	1.48
Treatments, Residuals not in Treatments	4		2113.72	528.43	7.74****
Residuals, Treatments not in Model	4		158.64	39.66	
Error, Residuals in Model	28		1912.58	68.31	
Error, Residuals not in Model	32		2317.40	72.42	
Totals	49		50793.10		

*p<.05
**p<.02
***p<.01
****p<.001

Table 24

Analysis of Variance, Arithmetic Total Accuracy[1]

(Experiment III)

Source of Variance	DF	SS	MS	F
Within Groups	5	57.22	11.44	5.84***
Between Groups	4	127.16	31.79	16.22****
Periods	4	145.15	36.29	18.52****
Treatments, Residuals not in Model	4	53.13	13.28	
Residuals, Treatments not in Residuals	4	11.32	2.83	1.44
Treatments, Residuals not in Treatments	4	43.35	10.84	5.53***
Residuals, Treatments not in Model	4	21.10	5.28	
Error, Residuals in Model	28	54.96	1.96	
Error, Residuals not in Model	32	66.28	2.07	
Totals	49	515.24		

[1]Number correct divided by number attempted.

*p<.05
**p<.02
***p<.01
****p<.001

Table 25

Mean Arithmetic Scores (Total Correct), Differences[1] and "t" Values (Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	176.47		0.48	2.61**	3.84****	0.31
Secobarbital	174.65	1.82		3.08***	4.32****	0.17
d-amphetamine, 10 mg.	186.38	- 9.90	-11.72		1.23	2.91***
d-amphetamine, 15 mg.	191.06	-14.59	-16.41	-4.69		4.15****
Placebo	175.31	1.16	- 0.66	11.07	15.75	

*p .05 - two-tailed test
**p .02
***p .01
****p .001

[1]Differences are column means minus row means.

Table 26

Mean Arithmetic Accuracy[1] (Totals),

Differences[2] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	92.21		3.70****	0.72	0.06	0.34
Secobarbital	89.84	2.37		2.98***	3.77****	4.05****
d-amphetamine, 10 mg.	91.95	0.46	-1.91		0.78	1.06
d-amphetamine, 15 mg.	92.25	-0.04	-2.41	-0.50		0.28
Placebo	92.43	-0.22	-2.59	-0.68	-0.18	

*p .05 - two-tailed test
**p .02
***p .01
****p .001

[1]Expressed as percentage correct of total attempted.

[2]Differences are column means minus row means.

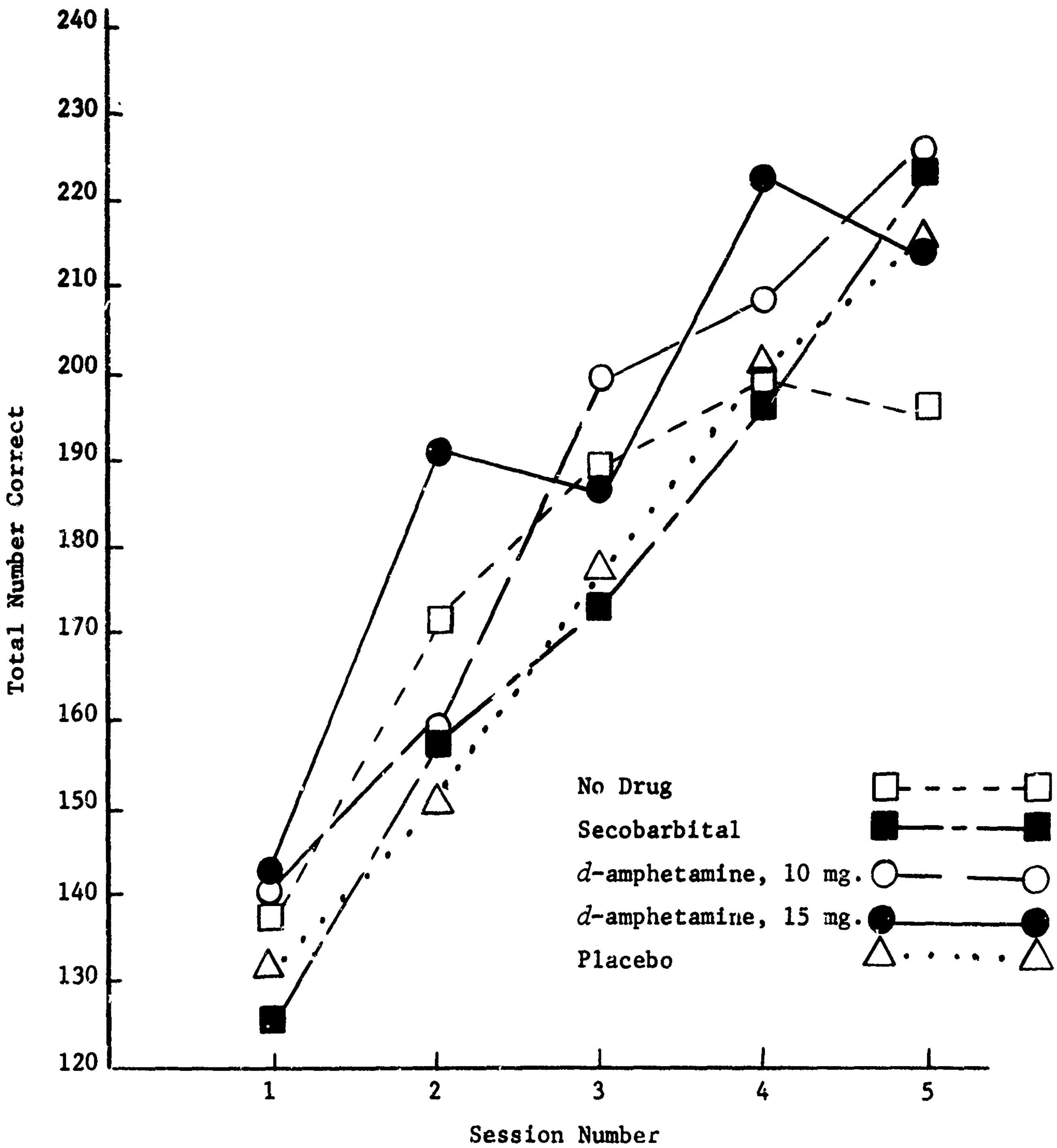

Fig. 14. Arithmetic Total Correct (Experiment III)

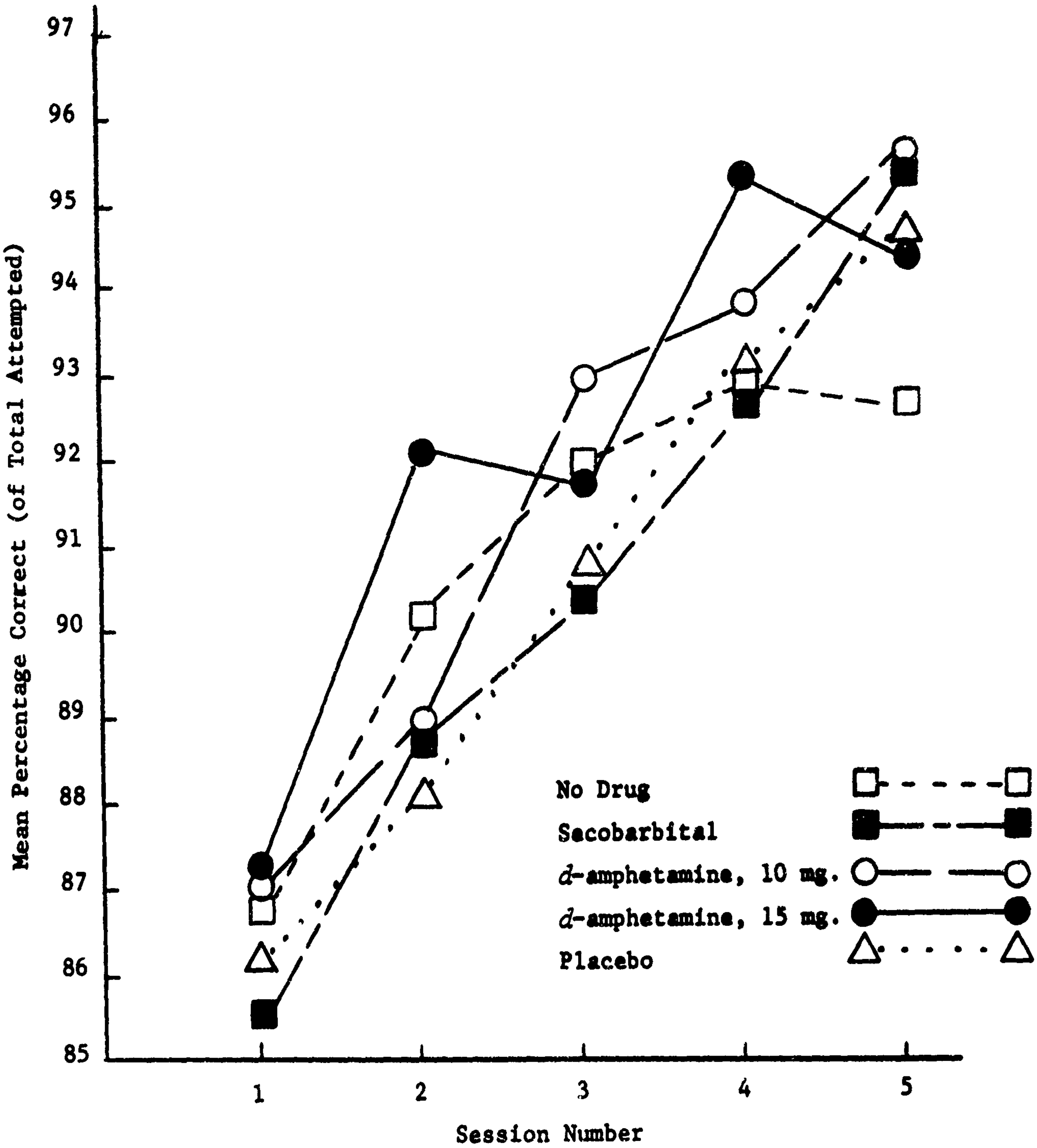

Fig. 15. Arithmetic Total Accuracy (Experiment III)

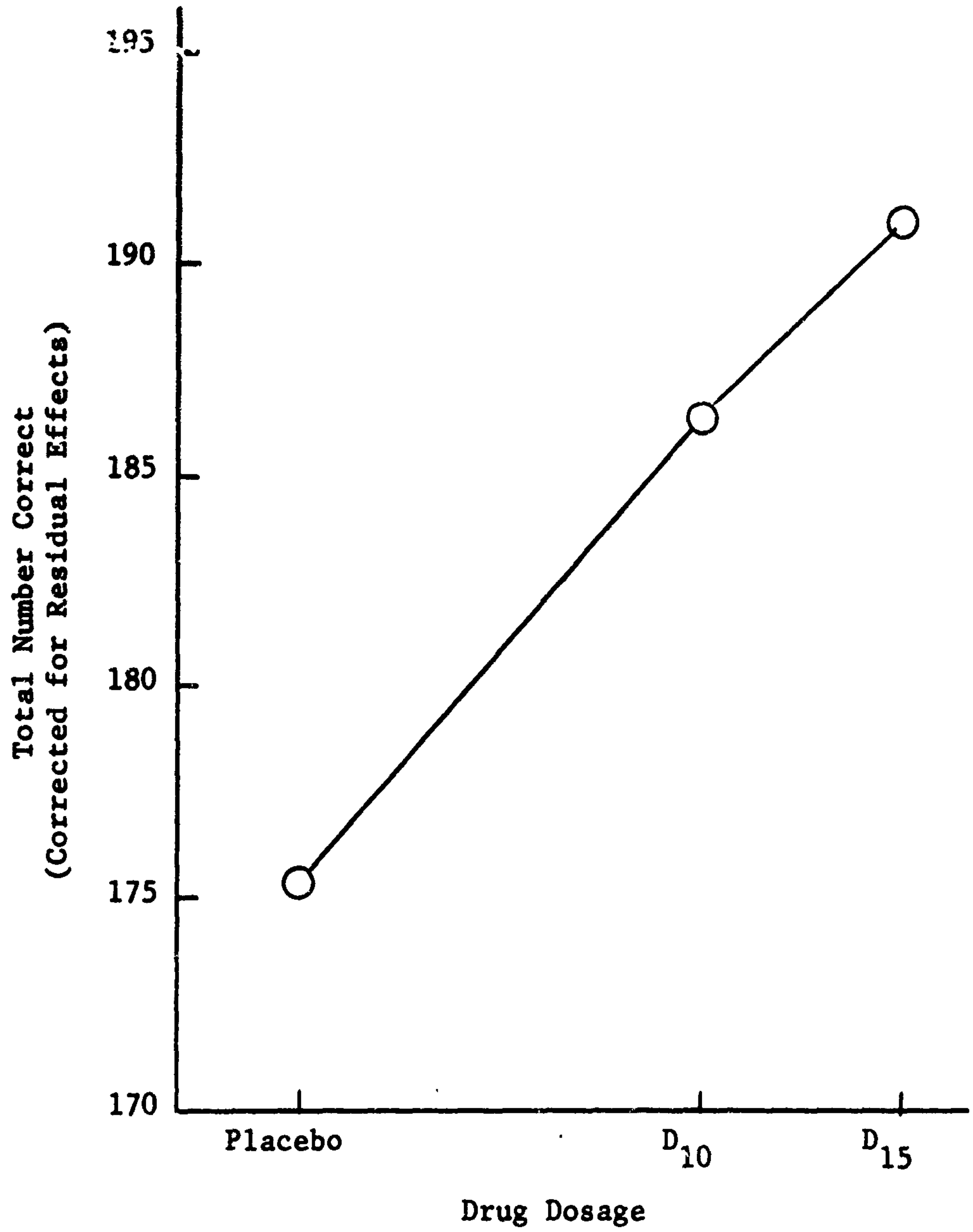

Fig. 16. Drug Dosage Curve: Arithmetic Speed

(Total Correct for All Problems Attempted)

(Experiment III)

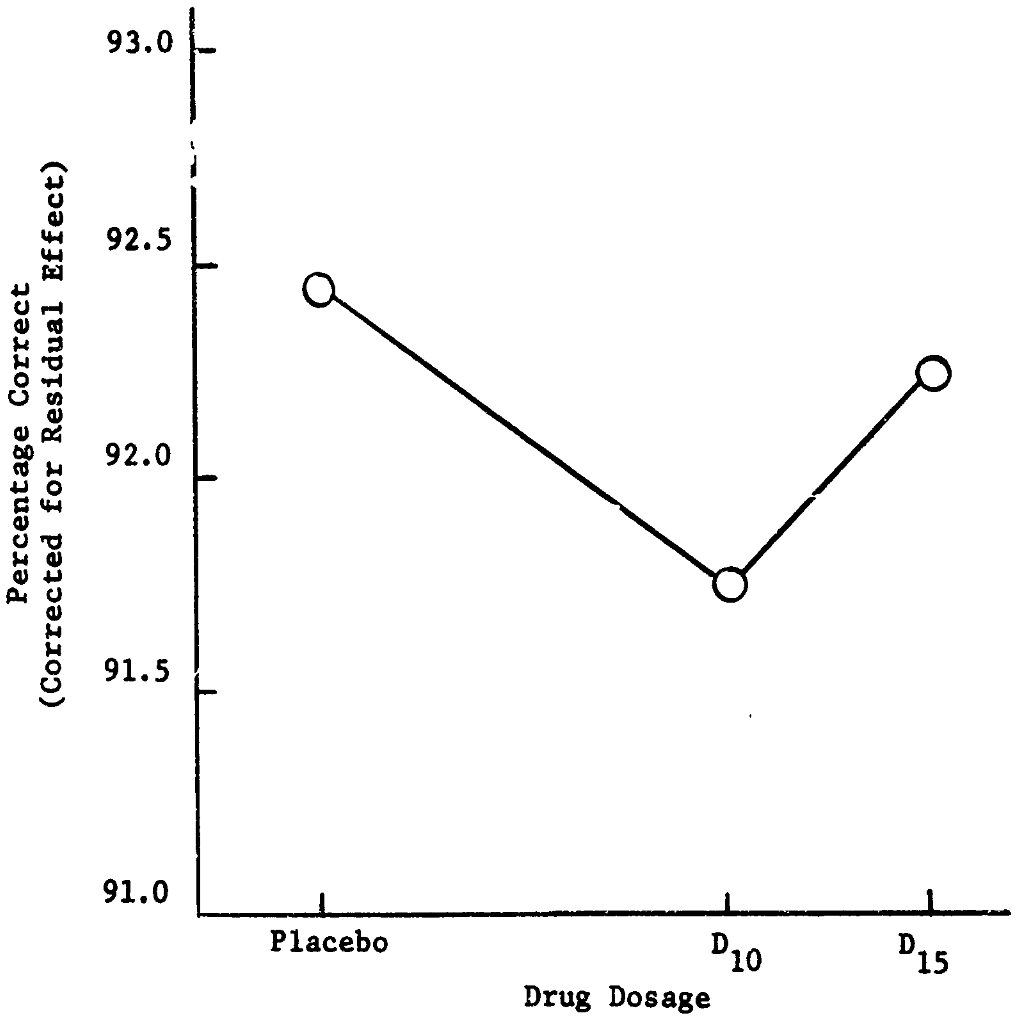

Fig. 17. Drug Dosage Curve: Arithmetic Accuracy

(Percentage Correct for All Problems Attempted)

(Experiment III)

gestion and the short duration of the hypnotic effect of secobarbital.

Turning to the "accuracy" findings, observe that the significance of the overall drug effect must be attributed mainly to accuracy reduction by S. The four paired comparisons involving this drug were highly significant, and were the only paired comparisons to approach statistical significance. Yet S was not significantly inferior to P or ND in total correct, while both D_{15} and D_{10} were significantly superior to P in total correct. Thus, increased work output at essentially constant accuracy gave D_{15} or D_{10} its superiority over P or ND, and increased work output compensated for diminished accuracy with S. This diminution became gradually more pronounced during the progress of the test.

As with the PSMT, the between periods effect was highly significant ($p<.001$). In addition, residual or "carryover" effects were not significant, although the correlation between direct and residual effects was even greater (+.88) and significant ($p<.05$).

Judgment of performance

No significant drug effects were obtained for performance judgment bias with either the PSMT or the arithmetic task. Mean biases (estimated percentage correct minus obtained percentage correct) are listed by drug condition for each task in Table 27. The F-ratios for drugs were 0.76 and 1.63 respectively, neither of which approaches the 2.71 value required for significance at the .05 level.

Mood (MACL) results

In the first administration of the MACL (at t_1 + 8 minutes),

Table 27

Judgment Bias

(Experiment III)

	Paced Sequential Memory Task		Arithmetic Task	
	Obtained Per Cent Correct	Under- or Over-Estimate (Per Cent)	Obtained Per Cent Correct*	Under- or Over-Estimate (Per Cent)
No Drug	48.77	-6.64	92.22	-8.92
Secobarbital 100 mg.	46.44	-8.37	89.84	-5.91
d-amphetamine 10 mg.	49.80	-6.07	91.75	-9.32
d-amphetamine 15 mg.	51.59	-6.17	92.25	-7.33
Placebo	48.53	-5.44	92.42	-8.89

*Number correct divided by number attempted.

significant F-ratios for drugs were obtained with the three of the eleven mood factors: "anxiety" ($p<.05$), "sociability" ($p<.01$), and "elation" ($p<.05$). A positive drug response within eight minutes of oral ingestion seems unlikely for secobarbital, and very unlikely for *d*-amphetamine. Considering the possibility that placebo effects were involved, separate t-tests were computed between paired means of drug conditions. The drug means, their differences, and the significances of these differences are listed for the three significant mood factors in Tables 28, 29, and 30.

The second MACL was included as a time-filler in the last four sessions only. Since the incomplete data would permit only weak between-subject comparisons, they were discarded.

The third MACL administration (at t_i + 115 minutes) significant F-ratios for "fatigue" ($p<.01$) and "elation" ($p<.001$) as shown in Table 31. Paired comparison data are presented in Tables 32 and 33. These data indicate fatigue reduction from D_{15} or D_{10}, and mildly suggest a fatigue increase from S. The overall significance of the "elation" results is largely attributable to the high means of D_{10} and D_{15}, with a suggestive contribution by S which reliably exceeded ND but had only a marginal advantage over P. Separate t-tests were computed for "vigor" and "boldness" even though their overall drug F-ratios did not reach significance. The selected comparisons, D_{10} vs. P and D_{15} vs. P, revealed that for boldness D_{10} showed a significant increase ($p<.05$) and D_{15} was borderline ($.05<p<.10$); for vigor, both tended in the predicted direction (increase) but were not significant (D_{15}: $.05<p<.10$). (See Tables 34 and 35.)

Table 28

Mood ACL #1: Mean Scores for Anxiety,

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	3.67		1.96†	0.17	2.61**	0.70
Secobarbital	4.12	-0.45		2.13*	0.65	1.26
d-amphetamine, 10 mg.	3.63	0.04	0.49		2.78***	0.87
d-amphetamine, 15 mg.	4.27	-0.60	-0.15	-0.64		1.91†
Placebo	3.83	-0.16	0.29	-0.20	0.44	

† .10
*p .05
**p .02
***p .01
****p .001

[1]Differences are column means minus row means.

Table 29

Mood ACL #1: Mean Scores for Sociability,

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	6.03		0.41	3.03***	0.24	0.52
Secobarbital	6.15	-0.12		2.62**	0.66	0.93
d-amphetamine, 10 mg.	6.91	-0.88	-0.76		3.28***	3.55***
d-amphetamine, 15 mg.	5.96	0.07	0.19	0.95		0.28
Placebo	5.88	0.15	0.27	1.03	0.08	

*p<.05
**p<.02
***p<.01

[1]Differences are column means minus row means.

Table 30

Mood ACL #1: Mean Scores for Elation,

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	4.51		0.93	2.46*	1.14	0.68
Secobarbital	4.77	-0.26		1.54	2.07*	0.25
d-amphetamine, 10 mg.	5.20	-0.69	-0.43		3.61***	1.79†
d-amphetamine, 15 mg.	4.19	0.32	0.58	1.01		1.82†
Placebo	4.70	-0.19	0.07	0.50	-0.51	

†p .10
*p .05
**p .02
***p .01

[1]Differences are column means minus row means.

Table 31

Mood ACL #3: Means by Drug Condition, F-Ratios and Significance Levels

(Experiment III)

Mood Factors	Drug						
	No Drug	Secobarbital	*d*-amphetamine 10 mg.	*d*-amphetamine 15 mg.	Placebo	F-Ratio	Significance Level
Aggression	3.97	3.70	3.96	3.97	4.18	0.61	--
Anxiety	3.63	3.64	3.64	4.07	3.75	0.68	--
Surgency	5.16	5.54	5.52	5.53	5.18	0.56	--
Concentration	7.12	6.78	7.31	7.09	6.91	0.61	--
Fatigue	6.22	7.11	5.45	5.30	6.61	4.22	0.01
Sociability	5.28	5.58	5.62	5.41	5.20	0.45	--
Sadness	3.87	3.89	3.68	3.67	3.55	1.00	--
Egotism	3.75	3.94	3.90	4.36	4.16	1.28	--
Elation	3.75	4.59	5.07	4.86	4.07	6.45	0.001
Vigor	4.94	5.22	5.81	5.92	5.14	2.13	--
Boldness	5.39	5.41	6.10	6.06	5.32	2.25	--

Table 32

Mood ACL #3: Mean Scores for Fatigue,
Differences[1] and "t" Values
(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	6.22		1.71†	1.48	1.77†	0.75
Secobarbital	7.11	-0.89		3.19***	3.48***	0.96
d-amphetamine, 10 mg.	5.45	0.77	1.66		0.29	2.23*
d-amphetamine, 15 mg.	5.30	0.92	1.81	0.15		2.52**
Placebo	6.61	-0.39	0.50	-1.16	-1.31	

†p<.10
*p<.05
**p<.02
***p<.01

[1]Differences are column means minus row means.

Table 33

Mood ACL #3: Mean Scores for Elation,

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	3.75		2.80***	4.40****	3.70****	1.07
Secobarbital	4.59	-0.84		1.60	0.90	1.73†
d-amphetamine, 10 mg.	5.07	-1.32	-0.48		0.70	3.33***
d-amphetamine, 15 mg.	4.86	-1.11	-0.27	0.21		2.63**
Placebo	4.07	-0.32	0.52	1.00	0.79	

†p<.10
*p<.05
**p<.02
***p<.01
****p<.001

[1]Differences are column means minus row means.

Table 34

Mood ACL #3: Mean Scores For Vigor,

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	4.94		0.67	2.07*	2.33*	0.48
Secobarbital	5.22	-0.28		1.40	1.67	0.19
d-amphetamine, 10 mg.	5.81	-0.87	-0.59		0.26	1.59
d-amphetamine, 15 mg.	5.92	-0.98	-0.70	-0.11		1.86†
Placebo	5.14	-0.20	0.08	0.67	0.78	

†p<.10
*p<.05

[1]Differences are column means minus row means.

Table 35

Mood ACL #3: Mean Scores for Boldness

Differences[1] and "t" Values

(Experiment III)

	Mean	ND	S	D-10	D-15	P
No Drug	5.40		0.03	1.89†	1.78†	0.22
Secobarbital	5.41	-0.01		1.86†	1.76†	0.24
d-amphetamine, 10 mg.	6.10	-0.70	-0.69		0.11	2.11*
d-amphetamine, 15 mg.	6.06	-0.66	-0.65	0.04		2.00†
Placebo	5.32	0.08	0.09	0.78	0.74	

†p<.10

*p<.05

[1]Differences are column means minus row means.

Time perception bias

Neither administration ($t_1 + 15$ or $t_1 + 120$) of the time perception test revealed any biasing influence attributable to drug conditions, ($F = .75$, $F = .80$, respectively). In the second administration, ND, D_{15}, D_{10}, and P produced slightly greater estimates of elapsed time than did S. (See Table 36.)

Drug-guessing

In general, the subjects showed little ability to guess, 3 1/2 hours after ingestion, what type of drug they had received--at least with regard to the conventional labels "stimulant," "depressant," or "tranquilizer," vs. no effect. A contingency coefficient (Siegel, 1956, p. 196-203) was calculated for the total of the five sessions, with "true" categories assumed to be as follows:

d-amphetamine sulfate, 10 mg. or 15 mg. = stimulant

sodium secobarbital, 100 mg. = depressant or tranquilizer

placebo = no effect

The contingency coefficient for these data was .24, which is statistically significant ($p < .02$). (See Table 37.)

Discussion

H1: There is little doubt that D_{15} improved total PSMT performance relative to D_{10}, S, P or ND, regardless of input rate. Thus, H1 was definitely confirmed.

H2: Results with D_{10}, although not exceeding P or ND at acceptable levels of significance, suggest a mild enhancement effect which supports

Table 36

Time Perception Bias[1]

(Experiment III)

First Administration

Drug Condition	Mean	ND	S	D-10	D-15	P
No Drug	3.83		-0.56	-0.60	-0.76	-0.22
Secobarbital, 100 mg.	3.27			-0.04	-0.20	0.34
d-amphetamine, 10 mg.	3.23				-0.15	0.39
d-amphetamine, 15 mg.	3.07					0.54
Placebo	3.61					

Second Administration

Drug Condition	Mean	ND	S	D-10	D-15	P
No Drug	3.59		-0.75	-0.39	-0.29	-0.44
Secobarbital, 100 mg.	2.84			0.36	0.46	0.31
d-amphetamine, 10 mg.	3.20				0.10	-0.05
d-amphetamine, 15 mg.	3.30					-0.15
Placebo	3.15					

[1]Bias = number of overestimates minus number of underestimates.

Differences are column means minus row means.

Table 37

Subjects' Estimates of Drug Received:

Contingency Table and Coefficient

(Experiment III)

Drug Received	Subjects' Estimates of Drug Received			
	Stimulant	Depressant or Tranquilizer	No Drug	Total
d-amphetamine (10 or 15 mg.)	27 (18.00)	42 (49.50)	26 (27.50)	95
Secobarbital	3 (8.91)	29 (24.49)	15 (13.61)	47
Placebo	6 (9.09)	28 (25.01)	14 (13.89)	48
Total	36	99	55	190

$X^2 = 12.02$ p .02

$C = 0.243$

but does not confirm H2. Support is furthered by two considerations:

1. A stronger and highly significant enhancement was obtained with D_{15}, a 50% higher dosage of the same drug.

2. The observed means for D_{10} exceeded P and ND by about 3% which is very close to the estimate inferred from the combined D_{10} results of Experiments I and II.

H3: Figure 12 reveals a sharper rise for D_{15} than for the other treatments between the first two 14-minute intervals of the PSMT. This could be interpreted as mitigation of fatigue/boredom. However, the failure of D_{15} to improve its relative position thereafter does not seem consistent with this explanation. It is possible that the low first-third results with D_{10} and D_{15} are due to an inadequate post-ingestion interval (70 to 84 minutes). This interpretation is, however, contrary to the results obtained in Experiment I, in which the only significant improvements occurred at about 1/2 hour shorter latency. Thus, there is no satisfactory explanation for these intra-period differences, and H3 remains to be further tested.

H4: The anti-stress viewpoint was moderately successful in predicting *inter*-period comparisons. With repeated weekly exposure to the PSMT, enhancement by D_{10} and D_{15} tended to decrease toward placebo levels (see Figure 11). Thus, increased practice with the PSMT seems to have precluded continued enhancement by *d*-amphetamine. This was predicted from the expectation that the stress-arousing effect of PSMT administration would undergo adaptation with repeated weekly exposure to the task. (Tachyphylaxis could scarcely be involved, since each subject received a given treatment only once.)

The anti-stress interpretation is strengthened by the tendency of the arithmetic t sk, which was presumably less stressful, to show a smaller decline in *d*-amphetamine enhancement.

Results from S, P or ND should be interpreted with some reservations because of the apparent differences in "learning curves" yielded by these medications. Although the composite learning curve in Figure 12 is classically well-behaved, the individual drug curves differ considerably in slope and acceleration. Thus, overall results with S, being significantly inferior to any other treatment, suggest that when this drug is given alone its direct cognitive depressant effects overwhelm any indirect benefits conferred by stress mitigation. This accords with the performance depression with barbiturates. Comparison of the "learning curves" suggests, however that the impairment effect of this drug is mitigated with repeated experimental sessions. This is, of course, a tentative conclusion, since the slopes of these "learning curves" are determined from between-group comparisons and therefore of low reliability. However, the graph shows a highly consistent improvement in the relative positions of the "secobarbital groups" as the series of weekly experiments progressed, suggesting that practice effects may protect a subject from depressant effects.

Results with P show no reliable difference when compared with ND. There is a suggestion in Figure 12 that a placebo effect may have been present, but that it was originally negative, later positive, and thus averages to about zero. This interpretation is strengthened by the consistent decline in position of ND relative to all of the active drugs, each of which of course involved a placebo effect.

An increasingly positive placebo effect might have resulted from increasing experience with the active drugs, whose subjective effects could have led to favorable expectations. This placebo phenomenon would account for some, but not all, of the increase in relative position of the secobarbital curve.

The results with the two input rate variations did not permit testing the effect of the "dropoff" phenomenon. Sharp increases in task-induced stress are expected to occur when speed/load conditions reach such levels as to effect accelerated reductions in subjects' information transfer rates. In the present study, the lower input rate produced about 43% correct. Correcting for guessing (rights minus wrongs) results in scores of approximately 52.5% and 40%. Multiplying the 0.40/0.525 ratio by the speed factor of 1.5 yields a ratio of 1.14. Thus the higher input rate produced greater information transfer, rather than a dropoff.

Arithmetic task findings

Correct answer totals were increased by D_{15} (relative to P or ND) to a degree comparable (in terms of percentage improvement or of statistical significance) with the PSMT enhancement. Thus, enhancement of this task with *d*-amphetamine does not depend upon prior induction of fatigue via sleep-deprivation as in Holliday's procedure (1964).

Although the arithmetic task, like the PSMT, was performed under incentive payoff conditions with a time limit, it was expected to be less stressful since it was self-paced. Thus, it might have been

expected to show less enhancement by D_{15} under the "anti-stress" hypothesis. Comparing percentages or levels of significance across tasks is like comparing apples with oranges. But in the absence of interval-scale information about underlying variables we must accept the parsimonious interpretation that the PSMT and arithmetic task *did* show roughly similar drug enhancement. Three interpretations are possible:

1. *D*-amphetamine has a general cognitive-enhancement influence that is largely independent of any differential weightings of task demands in the PSMT and the arithmetic task.

2. *D*-amphetamine has two or more drug-relevant component effects with regard to task demands, but the corresponding task demand components are proportionately weighted in the PSMT and the arithmetic task.

3. *D*-amphetamine has two or more component effects with regard to task demands, and the corresponding task demand components are disproportionately weighted in the PSMT and arithmetic tasks; however, the inequalities of the contributions to the different task-demand components are roughly balanced for these two tasks. Similar performance effects result from dissimilar causes.

Interpretation (1) implies a cognitive enhancing influence of *d*-amphetamine that is independent of pacing techniques, sensory modalities, task requirements (memorization vs. computation) and nature of test material (verbal vs. numerical). But a general failure to obtain enhancement from amphetamines, in a wide variety of cognitive tasks, has been reported (cf. Weiss and Laties, 1962). Thus, Interpretation (1) does not appear plausible.

Interpretation (2), implying proportionately weighted component task demands, may be attacked on similar grounds. The argument has already been presented that competing demands for recirculation and retrieval, coupled with rapid input pacing and especially with provision for working "in arrears," increases the stressfulness of a task. The high anxiety levels reported on the MACL between exposures to this task during Experiment I lend support to this contention. Furthermore, the self-pacing provision in the arithmetic task would seem to welcome an "energizing" component which would be of less utility in the PSMT.

Interpretation (3) requires the rather imparsimonious assumption that differential benefits from one component (e.g., a psychoanaleptic effect) were almost balanced by differential benefits from another component (e.g., an anti-stress effect). This assumption is, however, consistent with the following observations:

1. The dosage-response curves, although based upon only three points for each task, appear to be different. Comparison of PSMT totals (Figure 13) with arithmetic total correct (Figure 16) reveals that while the arithmetic curve is essentially linear, the PSMT curve is positively accelerated. This suggests a higher average dosage threshold for the anti-stress effects. (Recall that D_{10} generally failed to yield strong PSMT enhancement in Experiments I and II.)

2. In the arithmetic task, none of the superiority of D_{10} or D_{15} to P or ND in "total correct" could be accounted for in terms of increased accuracy; the entire enhancement was due to faster work output. This implies that an "energizing" component was responsible.

Recall, also, that this component appears to peak at a greater latency than the anti-stress effect and that the arithmetic task occurred 130 minutes after the completion of the PSMT. A similar interpretation would not appear to account for PSMT enhancement, since work output was paced by the input presentation rates. Nor could it be attributed to an increased willingness to guess.

It is not currently possible to choose with confidence among the foregoing interpretations. It is possible to devise some fairly crucial tests to facilitate this choice, and the resolution of the mechanisms by which drugs may enhance cognitive performance. These will be discussed in the last chapter.

The increased number of problems attempted under S might be attributable to an energizing component* similar to that suggested for D_{10} or D_{15}. However, it must be noted that the increase from S was achieved at the expense of significantly impaired accuracy. Thus, it may have been an "overconfidence" effect, as suggested by the significant overevaluations of performance produced by this drug in swimmers, (Smith and Beecher, 1960b) and the nonsignificant but parallel results with the calculus test (Smith and Beecher, 1964).

Referring to Figure 14 we see that the "total correct" arithmetic scores show progressive improvement over weekly intervals, in the relative position of the secobarbital curve. This confirms the corresponding observation with the PSMT. As with PSMT performance,

*This might appear unlikely in that secobarbital is widely employed to achieve an effect diametrically opposite to "psychoanaleptic." However, the arithmetic task was performed between 130 and 190 minutes after drug ingestion. At such latencies, the psycholeptic effect would be greatly weakened, and conceivably reversed, as by enzymatic compensation.

part of the relative improvement may well have been a placebo effect: The ND curve, again, progressively declines in position relative to placebo or to any of the active drugs.

Performance judgments

Failure of drug effects to approach significance confirms the results of Experiment II. This accords neither with the amphetamine-induced pessimism and secobarbital-induced optimism found by Smith and Beecher with swimmers (1960b) nor the amphetamine-induced optimism found by Smith and Beecher with calculus students (1964). It is evident that task requirements exert a strong moderating influence upon drug distortions of subjects' performance appraisals. The particular task dimensions involved in this moderating influence are not readily apparent.

These results fail to confirm the positive placebo effect ($p<.05$) upon performance judgments obtained in Experiment II, although the P-ND comparison shows a mild trend in this direction with the PSMT.

Mood effects

Results from the first MACL, administered only eight minutes post-ingestion, admit of no plausible interpretation. The three significant F-ratios (out of eleven mood factors) are not ascribable to placebo effects, since the ND means did not "straggle" from those of the four capsule treatments. The effects indicated for *d*-amphetamine would certainly not be expected at this latency; also, D_{10} and D_{15} results do not show consistent directionality. It would not appear reasonable to invoke other than a sampling effect explanation of these results.

The third MACL administration indicated fatigue reduction from D_{15} and D_{10}, as expected from the published data and our previous findings. The other significant mood effect, "elation," had not been found in our prior experiments with *d*-amphetamine, although this and other indices of "mood elevation" are frequent enough in the literature. The heightening of "anxiety" by D_{10} observed in Experiments I and II was not confirmed, although D_{15} showed a trend in this direction. Results with "vigor" and "boldness," significant only for selected comparisons of *d*-amphetamine treatments with placebo, show that "vigor" tended to reciprocate "fatigue" in a sensible manner, but "boldness" tended to parallel "anxiety," rather than to reciprocate it. This parallel relationship confirms the results of Smith and Beecher (1960a).

Time Judgments

Failure of drug effects upon time judgment to approach significance confirms the results of Experiment II. The discrepancies with Goldstone, Boardman, and Lhamon (1958) and Frankenhauser (1958) are thus firmly established, but permit no ready explanation.

The judgment to be rendered was the same in all these studies: "greater than one second" vs. "less than one second." In Goldstone, et al, the method of limits was employed, while the present authors used the method of constant stimuli. In all cases, the common reference value was stored in the subjects' memories. It is difficult to see how such procedural variations could account for the observed discrepancies.

Drug-guessing

The pronounced lack of ability to identify the drugs in terms of the conventional categories is interesting. The tendency to judge *d*-amphetamine as a depressant or tranquilizer is, of course, consistent with the hypothesis of an anti-stress component in amphetamines. However, there is a distinct bias running through these rather "noisy" judgmental data, as indicated by the fact that the placebo was judged depressant 19 times, a tranquilizer 9 times, and a stimulant only 6 times. This may have resulted from the demanding nature of the test situation, although Goldstone, et al, observed a tendency to attribute depressant properties to placebos in an experiment involving time estimation. Regardless of etiology, it would seem that if the depressant properties of the placebo component were scaled and used to "adjust," in some dubious manner, the *d*-amphetamine data, one should find that the transformed *d*-amphetamine judgments tended to express "stimulation." (D_{10} yielded twice as many "stimulation" responses as did placebo, and D_{15} yielded 2 1/2 times as many.) However, a similar transform applied to the secobarbital judgments would then indicate that 100 mg. of sodium secobarbital had no perceived effect on the stimulant-depressant dimension. (Secobarbital was judged a depressant or a tranquilizer 29 times, and placebo thus judged 28 times.) It may well be that different subjects were responding differentially to separate components of this drug's effect. Thus, a "disinhibitory" component may have suggested a stimulant, drowsiness a depressant, and anxiety reduction a tranquilizer.

The near-chance relationships between traditional drug categories and category judgments by naive subjects, as obtained in

Experiments II and III, have interesting implications. First, it is possible that there is no really pressing need, in *acute* medication studies, for use of "active placebos" to control suggestion phenomena due to recognition, by drug-naive subjects, of tell-tale symptoms. It may be, however, that part of the "noise" in category judgments resulted from the inadequacies of the categorical names and of their common-usage definitions.

Summary of Experiment III

This was the third experiment in a series designed to measure joint effects of drugs and task requirements upon task-induced stress. Dependent variables included performance at a paced sequential memory task (PSMT), judgment biases concerning this performance, and mood ratings on the Nowlis MACL.

The major hypotheses were derived from the postulate that amphetamines exert a specifically beneficial effect upon performance under high emotional stress, presumably due to a mood-relevant component distinct from their well established psychoanaleptic properties. Experiments I and II had tested various hypotheses derived from this viewpoint. The most important of these involved drug enhancement of performance of non-fatigued subjects in the PSMT under various "stressor" conditions. Results of these experiments were equivocal: Tendencies toward enhancement by *d*-amphetamine were observed generally but with low statistical reliability and inadequate predictability. The major purposes of Experiment III were (1) to confirm or refute these enhancement effects, (2) to explore dosage variations in *d*-amphetamine, (3) to determine the interaction of drug effects with PSMT pacing,

(4) to compare PSMT effects with those on a non-paced cognitive task without storage requirements, and (5) to determine the sensitivities of both tasks to a depressant drug.

Forty-eight paid student volunteers were randomly assigned to experimental sequences in a Latin square balanced for subject, periods, and residual effects. Five medications were administered on five evening sessions spaced by one-week intervals: (1) no drug, (2) sodium secobarbital, 100 mg., (3) *d*-amphetamine sulfate, 10 mg., (4) *d*-amphetamine sulfate, 15 mg., and (5) placebo. The last four medications were given in matched capsules. In each session, both the 42-minute PSMT and the 60-minute arithmetic task were performed under strong monetary incentives. A 30-minute interval between these tasks was occupied by the Nowlis Mood Adjective Check List (MACL), a time estimation task, and a 10-minute break. The entire procedure was designed to yield high task-induced "stress" and minimal boredom. Input pacing for the PSMT was varied in counterbalanced order within each test session. Measures of mood and performance level were obtained at regular intervals throughout. Self-appraisals of performance were obtained, and compared with actual performances to test for bias. Time judgments were also obtained. At the end of each session, subjects were required to indicate how their medications had affected them, according to the categories "stimulant," "depressant," "tranquilizer," and "no effect."

Significant ($p<.01$) enhancement of PSMT performance was obtained with 15 mg. *d*-amphetamine at both input speeds. The 10 mg. dosage of this drug yielded only a non-significant positive trend, comparable to the average results from the previous experiments. Significant

($p<.001$, $p<.01$) enhancement of arithmetic performance was obtained for the 15 mg. and the 10 mg. dosages, respectively, Secobarbital significantly depressed PSMT performance, and depressed arithmetic accuracy but not total correct. Its depressant effects tended to diminish toward placebo levels with repeated exposures to the tasks.

No significant drug effects were obtained for time estimation bias or performance self-appraisal bias. Both dosages of *d*-amphetamine reliably increased MACL ratings on the "elation" factor and decreased ratings on the "fatigue" factor.

The coefficient of concordance between actual drug categories and self-rated effects was .24 (non-significant).

The absence of significant drug-induced biases in time estimation was at variance with published data concerning amphetamines and secobarbital. This discrepancy did not yield to ready explanation. The absence of significant effects upon performance judgments adds to the present confusion in this area. It was suggested that certain task demand parameters may moderate any drug-induced tendencies toward optimistic or pessimistic self-appraisal.

PRACTICAL IMPLICATIONS

While widely varying in levels of statistical significance, the three experiments were consistent in the ordering of drug means for PSMT performance. *D*-amphetamine, whether alone or in combination with secobarbital or chlordiazepoxide, and whether in 10 mg. dosages or 15 mg. dosages, always produced better mean totals than placebo, no drug, or any other drug employed. Its margin of superiority over placebo or no drug was highly significant ($p<.01$) at the 15 mg.

dosage employed in Experiment III. Considered jointly, these findings leave little doubt that *d*-amphetamine enhances average PSMT performance. From Experiment III, we can also conclude that it very probably enhances arithmetic performance, even in a one-hour test session. There is equally little doubt that the *average* extent of enhancement in either case is not more than 3 to 7%, so that dramatic improvements would not be expected from administration of a fixed dosage to randomly chosen subjects.

The practical implications of this modest enhancement are another matter. As Smith and Beecher (1959, p.556) have suggested, small improvements can be quite worthwhile in some situations. Acute administration of such a relatively non-toxic drug is a rather simple matter. If the gain is independent of those produced by selection, training, and human engineering (matters yet to be established), it represents a bonus delivered on top of the gains produced by these costlier procedures. Secondly, there is some evidence (from the residual effect analysis of Experiment III) that transitory gains in performance are paralleled by more durable gains, perhaps caused by improved learning. Finally, it appears that enhancement by *d*-amphetamine, at least on the PSMT, is not limited to situations producing strong fatigue or boredom. This conclusion is supported by the following observations:

1. Sleep deprivation was never imposed, nor was there ever any preceding task except for one or two 5-minute perception tests and the 33-item MACL.

2. The PSMT sessions never lasted more than 48 minutes (42 minutes in Experiment III). Breakdown of PSMT results by 12- or 14-minute

intervals did not show any consistent trend suggesting that *d*-amphetamine owed its margin to the later stages of testing. Experiment I showed a contrary trend: The superiority of *d*-amphetamine over no drug was greater during the earlier phases of testing, and failed to reach significance during most of the later phases. In Experiment II, the performance curves for the various drugs were virtually parallel. In Experiment III, enhancement increased between the first and second periods, but leveled off between the second and third periods.

3. Although the incentive variable employed in the first two experiments yielded no significant main effects or interactions with drug treatments, the following trend was consistently shown by *d*-amphetamine, whether given alone or as part of a combination:

The comparison with undrugged subjects was always more favorable under variable payoff than under fixed payoff conditions. (Refer to Figures 2 and 3 and Table 8.) Recalling that variable payoff conditions always produced substantially higher anxiety ratings than did fixed payoff, this trend suggests that PSMT enhancement by *d*-amphetamine is greater with higher levels of anxiety or motivation. Thus, it appears indefensible to attribute the observed enhancement to mitigation of motivational deficiencies-- i.e., to anti-boredom properties.

4. Dosage-response results suggest a different component at work than that responsible for mitigation of fatigue/boredom. The latter type of result has been observed with as little as 5 mg. *d*-amphetamine by Hauty and Payne (1955) and with 10 mg. *dl*-amphetamine by Mackworth (1950). Yet PSMT performance shows scant (3%) increases with 10 mg. dosages of *d*-amphetamine, which approximately double when dosage is

increased to 15 mg.

Considered jointly, these observations argue for amending the conclusion of Weiss and Laties (1962, p.21), from published data available in 1961: "Neither the results of the simple nor the results of the complex tasks offer much hope of an affirmative answer to the question, 'Can drugs help to raise the level of 'intellectual' performance in normal subjects?'"

The "intellectual performance" referred to concerned "simple and complex verbal and arithmetic tasks" involved in the caffeine and amphetamine studies comprehensively reviewed by the authors.

While anti-fatigue and anti-boredom properties are undoubtedly possessed by amphetamines, the observed PSMT effects cannot be explained on this basis.

The validity of the alternative "anti-stress" interpretation, however, remains in doubt. Although the foregoing observations tend to support the postulate of an "anti-stress" component in *d*-amphetamine, some of our observations do not fit this interpretation so readily: Mainly, the lack of dependence of PSMT enhancement upon intra-session variations in $\overline{SL}$ (Experiments I and II) or input pacing rates (Experiment III). Also, a roughly comparable degree of enhancement was obtained in a non-paced arithmetic task administered later in each test session of Experiment III. Further study will be necessary to confirm or reject this or any other interpretation of *d*-amphetamine effects on PSMT performance.

IMPLICATIONS FOR FURTHER RESEARCH

The foregoing discussion has presented some implications for the use of drugs to enhance performance at "stressful" tasks. Such enhancement effects were demonstrated in certain specific situations. What remains is to explore the generality of these effects.

Objectives: Basic and Applied

That acute administration of *d*-amphetamine sulfate can enhance some types of cognitive performance in task-stressed subjects, without regard to the prior existence of fatigue or oxygen deprivation, may now be considered established. Before such a medication can be confidently applied in practice, however, it is necessary to conduct further explorations. These are, of course, the problems of physiological and behavioral toxicity. Weiss and Laties (196?) have summarized some convincing evidence that these problems are of minor importance with *acute* administration of amphetamines. The most compelling study need would seem to involve not the "cost" problem but the "moderator" problem: To what extent are enhancement effects a function of task dimensions, motivational variations, subject characteristics, and practice or training levels, as well as drug/dosage/latency variations? How do these influences interact with one another?

The research described above has, it is hoped, provided some directly useful information regarding some of these influences. A thorough elucidation of the "moderator" domain is another matter. The number of possible combinations of such variables is imposing. It precludes complete, systematic exploration by grossly empirical means, even with the aid of complex experimental designs. Generalizable

conclusions are necessary, and conclusions of any high generality require a theoretical structure. Thus, basic and practical considerations coincide: theory is a practical necessity.

A very general theoretical position has been elaborated in the foregoing chapters. Hypotheses derived from it have been formulated as testable predictions, and the tests performed. These hypotheses were derived intuitively. This procedure was necessitated by ignorance of the quantitative relationships among the parameters being manipulated. Thus, hypotheses could at best be written in terms of inequalities, and sometimes only in terms of relative inequalities.

Critical evaluation of this or any other theory addressed to predicting drug-enhancement phenomena requires quantification of certain relationships, sometimes as a *prerequisite* to proper hypothesis testing. The following is a discussion of some of these relationships. Each is discussed in terms of the operations for measuring it.

Dose-response phenomena

Data from published literature and from the experiments described above suggest that there are important differences in drug-enhancement thresholds among different types of tasks. Thus, the same drug (e.g., *d*-amphetamine) may under some conditions require rather large dosages, and under still other circumstances fail to enhance or even impair performance. Determination of such relationships would be of relevance to the present theory, as well as to the contentions of Barmack (1939), Eysenck (1963), Weiss and Laties (1962) and others.

In the discussion of our performance data, it was indicated that PSMT performance enhancement by *d*-amphetamine seems to have a rela-

tively high dosage threshold, or at least a steep dose-response curve, when compared with enhancement of performance in "mental fatigue" or "vigilance" situations. It was suggested that this might be due to differential loadings of "stress" and "boredom" factors in the various tasks, and differential dose-response curves for hypothesized "anti-stress" and "anti-boredom" components in this drug's effect. There are some questions which must be answered in order to confirm or reject this interpretation.

To begin with, any dose-response curve is dependent upon choice of units of response measurement. When we seek to interpret such a curve in terms of "underlying dimensions," we must be assured that measurement artifacts are not involved. An obvious example is the "ceiling effects" in performance measurement, which will inevitably result in diminishing marginal returns from any enhancing influence as the perfect score is approached. Such a ceiling would not appear to have been present with either the PSMT or the arithmetic task discussed above. PSMT performance averages did not exceed 70% in any of our experiments, and the arithmetic task was "open-ended." However, it is not possible to make valid comparisons of these dose-response curves with those obtained from "vigilance" tasks such as that of Hauty and Payne (1955), where near-perfection was obtained with 5 mg. *d*-amphetamine. Only "threshold" comparisons can be made, and these tend to be unreliable since absolute thresholds may not exist.

Perhaps the best strategy for such comparisons is to compare dose-response curves for energizing effects, in a number of open-

ended but relatively non-stressful tasks such as the arithmetic test, with those obtained in stress situations. Essentially, this would involve verification of the relationships obtained in Experiment III across a number of variations in presumably "irrelevant" task dimensions such as subject matter (verbal vs. numerical) and sensory mode of presentation (visual vs. auditory). Changes in dose-response curves produced by such variations would be compared with those produced by manipulating theoretically relevant dimensions such as requirements for simultaneous storage and retrieval, input pacing in the "dropoff" regions, etc.

Latency phenomena

In Experiment III, the PSMT always occupied the interval of 70 to 112 minutes after drug ingestion, and the arithmetic task the interval of 143 to 203 minutes after ingestion. If the general hypothesis be correct with regard to the relative roles of stress and fatigue-boredom in the two tasks, *and* if the latency of the anti-fatigue peak is indeed the shorter of the two, then it might be instructive to reverse the order of the two tasks. The degrees of enhancement from D_{10} and D_{15} might then be compared with those observed in Experiment III. Such a comparison could, however, be biased by the differential carry-over effects from one task to the other. A superior though costlier technique would involve separate administration of each task at varying intervals after drug administration, with interpolated rest periods. This would probably require the assignment of a separate group to each task, since each group would have to be retested with varying drug treatments to achieve a sufficiently powerful

experimental design.

Moderation by task parameters

In our three experiments, drug effects upon PSMT performance were uninfluenced by intra-session variations in $\overline{SL}$ or input rate. Yet the rarity of drug enhancement of cognitive performance, in the variety of situations studied, suggests that crucial task parameters do exist.

If stress mitigation is truly involved in the PSMT enhancement so far obtained, we must conclude that the variations in $\overline{SL}$ and pacing rates did not significantly alter the task's stressfulness. Nevertheless, these may be moderator parameters:

1. It may be that variations in speed/load demands are important only in the ranges where the task either becomes undemanding, and produces very little stress at all, or where the "dropoff" (sharp reduction of information transfer rate) occurs due to excessive, competing demands.

2. It may be that stress levels have fairly high temporal stability, so that short-term variations in pacing or $\overline{SL}$ are ineffective in moderating drug effects. (Recall that Holliday and Dille found that non-shock trials within a task registered more enhancement from meprobamate than did shock trials.) To test these interpretations, (1) an attempt should be made to reach the "dropoff" zone, and (2) pacing and $\overline{SL}$ should be varied over longer time intervals, preferably between test sessions with the various medications. Such variables could be manipulated on a permanent between-subject basis, or within-subjects by balancing with period effects (more powerful but more "iffy").

It would also be instructive to incorporate a self-paced version of the PSMT. For group testing, this would probably necessitate a shift to the visual modality, which might in itself produce significant changes in drug responsiveness. Thus, it would be necessary to compare self-paced with externally-paced results within the common (visual) modality. All of our work has involved use of the auditory modality for input presentation. The anti-stress viewpoint asserts that drug enhancement of PSMT results from influences upon emotional arousal, which implies sub-cortical mechanisms involving the hypothalamus or limbic system. Thus, the susceptibility of the PSMT to *d*-amphetamine enhancement would not be moderated by choice of modality and corresponding cortical-association area. However, if such enhancement results from direct cognitive facilitation, moderation might be obtained as a result of differential concentration of drug effects in various association areas. Alternative interpretations are possible, but research with other modalities would at any rate determine the practical generalizability of our findings. To construct a visual analog of the PSMT, a provision would have to be made for subjects to record their responses without preempting the visual channel, e.g., by use of a "touch system."

The effects of practice

The results of Experiment III suggested that cognitive enhancement by *d*-amphetamine diminished as the subjects became better acquainted with a task. This could have resulted from adaptation to stress arousal. It could also be that increasing mastery of relevant skills invokes an overlearning mechanism which not only "fixes" them with

regard to forgetting, but also reduces their ability with respect to drug influences. This could apply equally to enhancement or to impairment (recalling the secobarbital results).

Conclusive demonstration of such an effect, and of its generality, would have considerable practical significance. Perhaps cognitive drug-enhancement is not under any circumstances, obtainable in highly trained subjects. Perhaps similar principles moderate the *impairment* effects of depressant drugs such as alcohol, barbiturates, tranquilizers, etc. In this case, permissible dosages of such drugs at certain hazardous tasks might well be keyed to levels of experience.

Clarification of these matters might be attempted by administering drugs at various levels of practice, with other factors held constant. This is not entirely straightforward, since practice not only increases the fixation of skills but also tends to reduce apparent difficulty, thus affecting attitude toward the task. It also has the usual result of increasing scores on any performance index, which recalls the measurement problem introduced in connection with dose-response curves. Suppose, for example, that a particular drug increases the average test performance of untrained subjects from 30% to 50% correct responses, and that of highly trained subjects from 70% to 75% correct. Can it be concluded that the enhancing influence diminishes with training, even if 25% of the test items may be almost impossibly difficult? Item analyses may be used to eliminate this particular source of confusion, but many laboratory and operational tasks are not amenable to [illegible] analyses.

It is doubtful that the moderator influence of practice effects can ever be decisively quantified, especially since some of the

questions involved are "pseudo" questions resulting from semantic vagaries. Nevertheless, it is possible to advance the present state of knowledge concerning these influences.

Control over some distorting influences could be achieved by progressively increasing task demands as ability grows with practice. Thus, in the PSMT, input pacing or storage load requirements could be manipulated to maintain, in non-drugged subjects, a constant average percentage of correct responses. Practice curves yielded by various drug conditions could be compared with each other and with those obtained in Experiment III. This would help isolate the contributions of changes in units of measurement, task attitudes, etc.

Durations of performance changes

Comparisons of direct effects with first-order residual effects of the treatments given in Experiment III showed positive correlations, both for PSMT performance (non-significant) and for the arithmetic task (significant). These correlations suggested that performance enhancement by D_{10} or D_{15} may have involved some persistent effect such as increased skill development. This suggestion could be tested via learning experiments, in which repeated PSMT administrations under constant drug conditions to each group were followed by a "crossover" to changed drug conditions. Some investigators have reported significant results with amphetamines in learning experiments. Eysenck, Casey and Trouton (1957) reported faster gains in pursuit-rotor proficiency from 10 mg. *d*-amphetamine, and Franks and Trouton (1958) obtained hastening of eyeblink conditioning with this dosage. However, Weiss and Laties (1962) have pointed out that learning effects

were not conclusively established, since no performance comparisons were made after the drugs had worn off: i.e., the "crossover" feature was missing.

If performance enhancement derives from mitigation of fatigue/boredom or of "stress" disturbances, then enhanced learning might well be expected as a result of improved attention or the removal of emotional blocks.

Impairment by amphetamines

If the stress-mitigation hypothesis be correct, then there are probably some tasks in which cognitive performance will be *impaired* by anti-stress agents regardless of direct effects on cognitive processes. Recall that the beneficial effects upon performance under "stress" are attributed to emotional effects such as increased self-confidence. Such effects could well impair performance in a problem-solving situation which required the abandonment of unsuccessful strategics. This impairment would be evident in situations where the productivity of a strategy does not become readily apparent, but must rather be judged by the subject from incomplete feedback. Drug-induced feelings of optimism, self-confidence, etc. might well bias such judgments, and lead to impaired performance. Such an effect may well have been involved in Smith and Beecher's (1964) study of *dl*-amphetamine effects upon calculus students, who overrated their performances but actually suffered slight (non-significant) impairment.

Such a mechanism could be revealed in several ways, as follow:

1. Structure the task so as to permit direct measurement of the number of times a strategy is abandoned or revised, and the

length of time each strategy is actively pursued.

2. Contrast the tendency to change strategies within-problem to the tendency to change strategies between-problems. If an influence upon behavior variability *per se* is involved in a drug's effect, these measures should be affected in parallel manner. If the influence is mediated through changes in self-confidence, etc., then within-problem variability should be more affected than between-problem variability. The conviction that a strategy was correct for one problem (based upon self-confidence) would not necessarily lead to confidence that it was correct for the following problem.

3. Determine whether any drug-impairment effects thus obtained can be reversed by instruction and/or "guided training" in the use of the drugs. If the impairment is indeed due to drug-induced perseveration, it should be reversible: Preventive measures against excessive confidence in one's judgment should benefit drug groups more than placebo groups.

Consistency of individual differences in responses to medication

With any of the experimental designs now popular in psychopharmacology, it is impossible to determine which individual differences in response to a drug are real, and which are due to measurement errors. Between-groups comparisons do not yield such information. Test-retest designs such as the crossover, the Latin square, or randomized blocks (subjects) yield estimates of individual differences as main effects, but confound measurement error with any real treatment x subject interactions that may be present.

Exploratory studies such as Cuthbertson and Knox (1947) have yielded valuable information concerning the fact that some consis-

tency obtains, as revealed by repeated medication of particular subjects. The number of individuals so tested is too small to assess the frequency or average magnitude of such differences. Tentative implications are that these differences are of such a degree that a given drug may consistently enhance performance in some individuals and consistently impair it in others. For acute operational use of drugs, quantification of the consistency of such differences would be of real value. It would establish the limits of how much could be gained by pre-treatment screening of subjects to predict whose performance will be enhanced, and whose impaired, by a particular drug. Numercus investigators have already addressed the problem of predicting favorability of response to medication on the basis of personality factors, etc. Prior to determination of response reliability, over day-to-day variations in physiological state, we can have no prior idea of the potentialities of any such predictive schemes. Even after the fact, we cannot know whether the imperfections in predictive accuracy (which are usually notable) result from deficiencies in the predictor instrument, or merely from the inherent instability of what is being predicted.

When the response involved is something like "sustained clinical improvement," it is difficult to measure test-retest reliability. However, when the response is a performance index which may be obtained in a single medication session, such measurement can and should be done. The experimental design need not be complex. The only requirements that are at all unique consist of the need to give each subject a particular medication on two or more occasions and a different medication (e.g., placebo) on two or more other occasions.

Serial effects would, of course, be controlled on a between-subject basis, yet such a procedure has very rarely been followed in experiments with human subjects.

Potentialities for acute drug enhancement in operational situations would be further improved by the concurrent development of a predictor variable; namely, the prior response to the drug. The performance increment or decrement produced in a subject with a simulated operational task might help to predict the extent of operational gain or loss he will subsequently incur with this drug, and do so better than any currently available personality or physiological "trait" measure. This notion could be tested by measuring the consistency of the favorable or adverse drug response as the individual is tested in various tasks, under various stresses, etc. A further development would involve determining inter-drug correlations. If an individual receives unusual benefit from a particular "stimulant" drug is he therefore more likely to respond favorably to a "stimulant" of a different drug family? Will the correlation be better if "family" is based upon clinical categorization or upon pharmacodynamics? The answers to such questions should have basic, as well as practical significance.

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13. ABSTRACT

Three experiments were conducted to test an hypothesis concerning drug enhancement of performance under task-induced stress. Cognitive abilities subjected to examination were highly paced short-term memory and simple arithmetic skill. Changes in mood state, judgment of performance and perception of time passage completed the behavioral characteristics assessed.

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UNCLASSIFIED

Security Classification

14. KEY WORDS	LINK A ROLE	LINK A WT	LINK B ROLE	LINK B WT	LINK C ROLE	LINK C WT
Stress						
Pacing						
Memory						
Drugs						
Incentives						
D-amphetamine						
Secobarbital						
Methylphenidate						
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